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<p>(54) Title: SYNTHETIC PEPTIDE INHIBITORS OF HIV TRANSMISSION (57) Abstract The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP-178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1_{LAI} gp41 protein, and fragments, analogs and homologs of DP-178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.</p>		

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SYNTHETIC PEPTIDE INHIBITORS OF HIV TRANSMISSION1. INTRODUCTION

The present invention relates to DP-178 (SEQ ID:1), a peptide corresponding to amino acids 638 to 673 of the HIV-1_{LAI} transmembrane protein (TM) gp41, and portions, analogs, and homologs of DP-178 (SEQ ID:1), all of which exhibit anti-viral activity. Such anti-viral activity includes, but is not limited to, the inhibition of HIV transmission to uninfected CD-4⁺ cells. Further, the invention relates to the use of DP-178 (SEQ ID:1) and DP-178 fragments and/or analogs or homologs as inhibitors of human and non-human retroviral, especially HIV, transmission to uninfected cells. Still further, the invention relates to the use of DP-178 as a HIV subtype-specific diagnostic. The present invention also relates to antiviral peptides analogous to DP-107, a peptide corresponding to amino acids 558 to 595 of the HIV-1_{LAI} transmembrane protein (TM) gp41, that are present in other enveloped viruses. The present invention further relates to methods for identifying antiviral compounds that disrupt the interaction between DP-178 and DP-107, and/or between DP-107-like and DP-178-like peptides. The invention is demonstrated by way of a working example wherein DP-178 (SEQ ID:1), and a peptide whose sequence is homologous to DP-178 are each shown to be potent, non-cytotoxic inhibitors of HIV-1 transfer to uninfected CD-4⁺ cells. The invention is further demonstrated by working examples wherein peptides having antiviral and/or structural similarity to DP-107 and DP-178 are identified.

2. BACKGROUND OF THE INVENTION

2.1. THE HUMAN IMMUNODEFICIENCY VIRUS

The human immunodeficiency virus (HIV) has been implicated as the primary cause of the slowly degenerative immune system disease termed acquired
5 immune deficiency syndrome (AIDS) (Barre-Sinoussi, F. et al., 1983, Science 220:868-870; Gallo, R. et al., 1984, Science 224:500-503). there are at least two distinct types of HIV: HIV-1 (Barre-Sinoussi, F. et al., 1983, Science 220:868-870; Gallo R. et al., 1984,
10 Science 224:500-503) and HIV-2 (Clavel, F. et al., 1986, Science 233:343-346; Guyader, M. et al., 1987, Nature 326:662-669). Further, a large amount of genetic heterogeneity exists within populations of each of these types. Infection of human CD-4⁺ T-
15 lymphocytes with an HIV virus leads to depletion of the cell type and eventually to opportunistic infections, neurological dysfunctions, neoplastic growth, and ultimately death.

HIV is a member of the lentivirus family of
20 retroviruses (Teich, N. et al., 1984, RNA Tumor Viruses, Weiss, R. et al., eds., CSH-Press, pp. 949-956). Retroviruses are small enveloped viruses that contain a diploid, single-stranded RNA genome, and replicate via a DNA intermediate produced by a
25 virally-encoded reverse transcriptase, an RNA-dependent DNA polymerase (Varmus, H., 1988, Science 240:1427-1439). Other retroviruses include, for example, oncogenic viruses such as human T-cell leukemia viruses (HTLV-I, -II, -III), and feline
30 leukemia virus.

The HIV viral particle consists of a viral core, composed of capsid proteins, that contains the viral RNA genome and those enzymes required for early
35 replicative events. Myristylated Gag protein forms an

outer viral shell around the viral core, which is, in turn, surrounded by a lipid membrane envelope derived from the infected cell membrane. The HIV envelope surface glycoproteins are synthesized as a single 160 Kd precursor protein which is cleaved by a cellular protease during viral budding into two glycoproteins, gp41 and gp120. gp41 is a transmembrane protein and gp120 is an extracellular protein which remains non-covalently associated with gp41, possibly in a trimeric or multimeric form (Hammarskjold, M. and Rekosh, D., 1989, Biochem. Biophys. Acta 989:269-280).

HIV is targeted to CD-4⁺ cells because the CD-4 cell surface protein acts as the cellular receptor for the HIV-1 virus (Dalglish, A. *et al.*, 1984, Nature 312:763-767; Klatzmann *et al.*, 1984, Nature 312:767-768; Maddon *et al.*, 1986, Cell 47:333-348). Viral entry into cells is dependent upon gp120 binding the cellular CD-4⁺ receptor molecules (McDougal, J.S. *et al.*, 1986, Science 231:382-385; Maddon, P.J. *et al.*, 1986, Cell 47:333-348) and thus explains HIV's tropism for CD-4⁺ cells, while gp41 anchors the envelope glycoprotein complex in the viral membrane.

2.2. HIV TREATMENT

HIV infection is pandemic and HIV associated diseases represent a major world health problem. Although considerable effort is being put into the successful design of effective therapeutics, currently no curative anti-retroviral drugs against AIDS exist. In attempts to develop such drugs, several stages of the HIV life cycle have been considered as targets for therapeutic intervention (Mitsuya, H. *et al.*, 1991, FASEB J. 5:2369-2381). For example, virally encoded reverse transcriptase has been one focus of drug development. A number of reverse-transcriptase-

targeted drugs, including 2',3'-dideoxynucleoside analogs such as AZT, ddI, ddC, and d4T have been developed which have been shown to be active against HIV (Mitsuya, H. et al., 1991, Science 249:1533-1544). While beneficial, these nucleoside analogs are not
5 curative, probably due to the rapid appearance of drug resistant HIV mutants (Lander, B. et al., 1989, Science 243:1731-1734). In addition, the drugs often exhibit toxic side effects such as bone marrow suppression, vomiting, and liver function
10 abnormalities.

Attempts are also being made to develop drugs which can inhibit viral entry into the cell, the earliest stage of HIV infection. Here, the focus has thus far been on CD4, the cell surface receptor for
15 HIV. Recombinant soluble CD4, for example, has been shown to inhibit infection of CD-4⁺ T-cells by some HIV-1 strains (Smith, D.H. et al., 1987, Science 238:1704-1707). Certain primary HIV-1 isolates, however, are relatively less sensitive to inhibition
20 by recombinant CD-4 (Daar, E. et al., 1990, Proc. Natl. Acad. Sci. USA 87:6574-6579). In addition, recombinant soluble CD-4 clinical trials have produced inconclusive results (Schooley, R. et al., 1990, Ann. Int. Med. 112:247-253; Kahn, J.O. et al., 1990, Ann.
25 Int. Med. 112:254-261; Yarchoan, R. et al., 1989, Proc. Vth Int. Conf. on AIDS, p. 564, MCP 137).

The late stages of HIV replication, which involve crucial virus-specific secondary processing of certain viral proteins, have also been suggested as possible
30 anti-HIV drug targets. Late stage processing is dependent on the activity of a viral protease, and drugs are being developed which inhibit this protease (Erickson, J., 1990, Science 249:527-533). The

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clinical outcome of these candidate drugs is still in question.

Attention is also being given to the development of vaccines for the treatment of HIV infection. The HIV-1 envelope proteins (gp160, gp120, gp41) have been shown to be the major antigens for anti-HIV antibodies present in AIDS patients (Barin, et al., 1985, Science 228:1094-1096). Thus far, therefore, these proteins seem to be the most promising candidates to act as antigens for anti-HIV vaccine development. To this end, several groups have begun to use various portions of gp160, gp120, and/or gp41 as immunogenic targets for the host immune system. See for example, Ivanoff, L. et al., U.S. Pat. No. 5,141,867; Saith, G. et al., WO 92/22,654; Shafferman, A., WO 91/09,872; Formoso, C. et al., WO 90/07,119. Clinical results concerning these candidate vaccines, however, still remain far in the future.

Thus, although a great deal of effort is being directed to the design and testing of anti-retroviral drugs, a truly effective, non-toxic treatment is still needed.

3. SUMMARY OF THE INVENTION

The present invention relates to DP-178 (SEQ ID:1), a 36-amino acid synthetic peptide corresponding to amino acids 638 to 673 of the transmembrane protein (TM) gp41 from the HIV-1 isolate LAI, which exhibits potent anti-HIV-1 activity. As evidenced by the example presented below, in Section 6, the DP-178 (SEQ ID:1) anti-viral activity is so high that, on a weight basis, no other known anti-HIV agent is effective at concentrations as low as those at which DP-178 (SEQ ID:1) exhibits its inhibitory effects. The invention further relates to those portions, analogs, and

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homologs of DP-178 which also show such antiviral activity. The antiviral activity of such DP-178 portions, analogs, and homologs, includes, but is not limited to the inhibition of HIV transmission to uninfected CD-4⁺ cells. The invention relates to the use of DP-178 (SEQ ID:1) and DP-178 fragments and/or analogs or homologs. Such uses may include, but are not limited to, the use of the peptides as inhibitors of human and non-human retroviral, especially HIV, transmission to uninfected cells, and as type and/or subtype-specific diagnostic tools.

An embodiment of the invention is demonstrated below wherein an extremely low concentration of DP-178 (SEQ ID:1), and very low concentrations of a DP-178 homolog (SEQ ID:3) are shown to be potent inhibitors of HIV-1 mediated CD-4⁺ cell-cell fusion (*i.e.*, syncytial formation) and infection of CD-4⁺ cells by cell-free virus. Further, it is shown that DP-178 (SEQ ID:1) is not toxic to cells, even at concentrations 3 logs higher than the inhibitory DP-178 (SEQ ID:1) concentration.

The invention also relates to analogous DP178 peptides in other enveloped viruses that demonstrate similar antiviral properties.

The invention further relates to peptides analogous to DP-107, a peptide corresponding to amino acids 558-595 of the HIV-1_{LA1} transmembrane protein (TM) of gp41, that are present in other enveloped viruses, and demonstrate antiviral properties. The present invention is based, in part, on the surprising discovery that the DP-107 and DP-108 domains of the gp41 protein non-covalently complex with each other, and that their interaction is necessary for the normal activity of the virus. The invention, therefore, further relates to methods for identifying antiviral

compounds that disrupt the interaction between DP-107 and DP-178, and/or between DP-107-like and DP-178-like peptides.

Embodiments of the invention are demonstrated, below, wherein peptides having structural and/or
5 similarity to DP-107 and DP-178 are identified.

3.1. DEFINITIONS

Peptides are defined herein as organic compounds comprising two or more amino acids covalently joined
10 by peptide bonds. Peptides may be referred to with respect to the number of constituent amino acids, i.e., a dipeptide contains two amino acid residues, a tripeptide contains three, etc. Peptides containing
15 ten or fewer amino acids may be referred to as oligopeptides, while those with more than ten amino acid residues are polypeptides.

Peptide sequences defined herein are represented by one-letter symbols for amino acid residues as follows:

20 A (alanine)
R (arginine)
N (asparagine)
D (aspartic acid)
C (cysteine)
25 Q (glutamine)
E (glutamic acid)
G (glycine)
H (histidine)
I (isoleucine)
30 L (leucine)
K (lysine)
M (methionine)
F (phenylalanine)
P (proline)
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S (serine)
 T (threonine)
 W (tryptophan)
 Y (tyrosine)
 V (valine)

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4. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Amino acid sequence of DP-178 (SEQ ID:1) derived from HIV_{LAI}; DP-178 homologs derived from HIV-1_{SF2} (DP-185; SEQ ID:3), HIV-1_{RF} (SEQ ID:4), and
 10 HIV-1_{MN} (SEQ ID:5); DP-178 homologs derived from amino acid sequences of two prototypic HIV-2 isolates, namely, HIV-2_{rod} (SEQ ID:6) and HIV-2_{NH2} (SEQ ID:7); control peptides: DP-180 (SEQ ID:2), a peptide incorporating the amino acid residues of DP-178 in a
 15 scrambled sequence; DP-118 (SEQ ID:10) unrelated to DP-178, which inhibits HIV-1 cell free virus infection; DP-125 (SEQ ID:8), unrelated to DP-178, was also previously shown to inhibit HIV-1 cell free virus infection (Wild et al., 1992, Proc. Natl. Acad. Sci
 20 USA 89:10,537-10,541); DP-116 (SEQ ID:9), unrelated to DP-178 had previously been shown to be negative for inhibition of HIV-1 infection using the cell-free virus infection assay (Wild, et al., 1992, Proc. Natl. Acad. Sci USA 89:10,537-10,541). Throughout the
 25 figures, the one letter amino acid code is used.

FIG. 2. Inhibition of HIV-1 cell-free virus infection by synthetic peptides. IC50 refers to the concentration of peptide that inhibits RT production from infected cells by 50% compared to the untreated
 30 control. Control: the level of RT produced by untreated cell cultures infected with the same level of virus as treated cultures.

FIG. 3. Inhibition of HIV-1 and HIV-2 cell-free virus infection by the synthetic peptide DP-178 (SEQ
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ID:1). IC50: concentration of peptide that inhibits RT production by 50% compared to the untreated control. Control: Level of RT produced by untreated cell cultures infected with the same level of virus as treated cultures.

5 FIG. 4A. Fusion Inhibition Assay. DP-178 (SEQ ID:1) inhibition of HIV-1 prototypic isolate-mediated syncytia formation. Data represents the number of virus-induced syncytia per cell.

10 FIG. 4B. Fusion Inhibition Assay. DP-180 (SEQ ID:2): scrambled control peptide. DP-185 (SEQ ID:3): DP-178 homolog derived from HIV-1_{SP2} isolate. Control: number of syncytia produced in the absence of peptide.

15 FIG. 5. Fusion inhibition assay: HIV-1 vs. HIV-2. Data represents the number of virus-induced syncytia per well. ND: not done.

 FIG. 6. Cytotoxicity study of DP-178 (SEQ ID:1) and DP-116 (SEQ ID:9) on CEM cells. Cell proliferation data is shown.

20 FIG. 7. Schematic representation of HIV-gp41 and maltose binding protein (MBP)-gp41 fusion proteins. DP107 and DP178 are synthetic peptides based on the two putative helices of gp41. The letter P in the DP107 boxes denotes an Ile to Pro mutation at amino acid number 578. Amino acid residues are
25 numbered according to Meyers et al., Human Retroviruses and AIDS, 1991, Theoret. Biol. and Biophys. Group, Los Alamos Natl. Lab., Los Alamos, NM.

 FIG. 8. A point mutation alters the conformation and anti-HIV activity of M41.

30 FIG. 9. Abrogation of DP178 anti-HIV activity. Cell fusion assays were carried out in the presence of 10 nM DP178 and various concentrations of M41Δ178 or M41PA178.

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FIG. 10. Binding of DP178 to leucine zipper of gp41 analyzed by ELISA.

FIG. 11A-B. Models for a structural transition in the HIV-1 TM protein. Two models are proposed which indicate a structural transition from a native oligomer to a fusogenic state following a trigger event (possibly gp120 binding to CD4). Common features of both models include (1) the native state is held together by noncovalent protein-protein interactions to form the heterodimer of gp120/41 and other interactions, principally through gp41 interactive sites, to form homo-oligomers on the virus surface of the gp120/41 complexes; (2) shielding of the hydrophobic fusogenic peptide at the N-terminus (F) in the native state; and (3) the leucine zipper domain (DP107) exists as a homo-oligomer coiled coil only in the fusogenic state. The major differences in the two models include the structural state (native or fusogenic) in which the DP107 and DP178 domains are complexed to each other. In the first model (A; FIG. 11A) this interaction occurs in the native state and in B during the fusogenic state. When triggered, the fusion complex in the model depicted in (A) is generated through formation of coiled-coil interactions in homologous DP107 domains resulting in an extended α -helix. This conformational change positions the fusion peptide for interaction with the cell membrane. In the second model (B; FIG. 11B), the fusogenic complex is stabilized by the association of the DP178 domain with the DP107 coiled-coil.

FIG. 12. Motif design using heptad repeat positioning of amino acids of known coiled-coils.

FIG. 13. Motif design using proposed heptad repeat positioning of amino acids of DP-107 and DP-178.

FIG. 14. Hybrid motif design crossing GCN4 and DP-107.

FIG. 15. Hybrid motif design crossing GCN4 and DP-178.

5 FIG. 16. Hybrid motif design 107x178x4, crossing DP-107 and DP-178. This motif was found to be the most consistent at identifying relevant DP-107-like and DP-178-like peptide regions.

10 FIG. 17. Hybrid motif design ALLMOTI5, crossing GCN4, DP-107, and DP-178.

FIG. 18. Hybrid motif design crossing GCN4, DP-107, DP-178, c-Fos c-Jun, c-Myc, and Flu Loop 36.

FIG. 19. Motifs designed to identify N-terminal proline-leucine zipper motifs.

15 FIG. 20. Search results for HIV-1 (BRU isolate) envelope protein gp41. Sequence search motif designations: Spades (♠): 107x178x4; Hearts (♥) ALLMOTI5; Clubs (♣): PLZIP; Diamonds (♦): transmembrane region (the putative transmembrane domains were identified using a PC/Gene program
20 designed to search for such peptide regions). Asterisk (*): Lupas method. The amino acid sequences identified by each motif are bracketed by the respective characters. Representative sequences chosen based on all searches are underlined and in
25 bold. DP-107 and DP-178 sequences are marked, and additionally double-underlined and italicized.

30 FIG. 21. Search results for human respiratory syncytial virus (RSV) strain A2 fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

FIG. 22. Search results for simian immunodeficiency virus (SIV) envelope protein gp41 (AGM3 isolate). Sequence search motif designations are as in FIG. 20.

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FIG. 23. Search results for canine distemper virus (strain Onderstepoort) fusion glycoprotein 1. Sequence search motif designations are as in FIG. 20.

5 FIG. 24. Search results for newcastle disease virus (strain Australia-Victoria/32) fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

10 FIG. 25. Search results for human parainfluenza 3 virus (strain NIH 47885) fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

15 FIG. 26. Search results for influenza A virus (strain A/AICHI/2/68) hemagglutinin precursor HA2. Sequence search designations are as in FIG. 20.

20 FIG. 27. Coiled-coil structural similarity and anti-RSV antiviral activity of 35-mer peptides synthesized utilizing the sequence of a 48-amino acid RSV F2 peptide which spans sequences identified utilizing the computer-assisted searches described herein. For the exact location and motifs utilized, see FIG. 21. "+" symbols are relative indicators of either structural similarity or antiviral activity, with a greater number of "+" symbols indicating a higher relative similarity or antiviral activity.

25 FIG. 28. Coiled-coil structural similarity and anti-RSV antiviral activity of 35-mer peptides synthesized utilizing the sequence of a 53-amino acid RSV F1 peptide which spans sequences identified utilizing the computer-assisted searches described herein. See FIG. 21 for the exact location and motifs used. "+" symbols are as described for FIG. 27.

30 FIG. 29. Coiled-coil structural similarity and anti-human parainfluenza 3 virus (HPF3) antiviral activity of 35-mer peptides synthesized utilizing the
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sequence of a 56-amino acid HPF3 peptide which spans sequences identified utilizing computer-assisted searches described herein. For the exact location and motifs utilized, see FIG. 25. "+" symbols are as described in FIG. 27.

5 FIG. 30. Coiled-coil structural similarity and anti-HPF3 antiviral activity of 35-mer peptides synthesized utilizing the sequence of a 70-amino acid HPF3 peptide which spans sequences identified
10 utilizing the computer-assisted searches described herein. For the exact location and motifs utilized, see FIG. 25. "+" symbols are as described in FIG. 27.

5. DETAILED DESCRIPTION OF THE INVENTION

Described herein are peptides that exhibit potent
15 antiviral activity. These peptides include DP-178 (SEQ ID:1), a gp41-derived 36 amino acid peptide, fragments and/or analogs of DP-178, and peptides which are homologous to DP-178. In addition, these peptides may include peptides exhibiting anti-viral activity
20 which are analogous to DP-107, a 38 amino acid peptide corresponding to residues 558 to 595 of the HIV-1_{LAI} transmembrane (TM) gp41 protein, and which are present in other enveloped viral proteins. Also described here are assays for testing the antiviral activities
25 of such peptides. The present invention is based, in part, of the surprising discovery that the DP-107 and DP-178 domains of the gp41 protein complex with each other via non-covalent protein-protein interactions which are necessary for normal activity of the virus.
30 As such, methods are described for the identification of antiviral compounds that disrupt the interaction between DP-107 and DP-178 peptides, and between DP-107-like and DP-178-like peptides. Finally, the use of the peptides of the invention as inhibitors of non-
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human and human viral and retroviral, especially HIV, transmission are detailed, as is the use of the peptides as diagnostic indicators of the presence of specific, viruses, especially retroviruses.

While not limited to any theory of operation, the following model is proposed to explain the potent anti-HIV activity of DP178, based, in part, on the experiments described in the working examples, *infra*. In the viral protein, gp41, DP178 corresponds to a putative α -helix region located in the C-terminal end of the gp41 ectodomain, and appears to associate with a distal site on gp41 whose interactive structure is influenced by the leucine zipper motif, a coiled-coil structure, referred to as DP107. The association of these two domains may reflect a molecular linkage or "molecular clasp" intimately involved in the fusion process. It is of interest that mutations in the C-terminal α -helix motif of gp41 (*i.e.*, the D178 domain) tend to enhance the fusion ability of gp41, whereas mutations in the leucine zipper region (*i.e.*, the DP107 domain) decrease or abolish the fusion ability of the viral protein. It may be that the leucine zipper motif is involved in membrane fusion while the C-terminal α -helix motif serves as a molecular safety to regulate the availability of the leucine zipper during virus-induced membrane fusion.

On the basis of the foregoing, two models are proposed of gp41-mediated membrane fusion which are schematically shown in FIG. 11A-B. The reason for proposing two models is that the temporal nature of the interaction between the regions defined by DP107 and DP178 cannot, as yet, be pinpointed. Each model envisions two conformations for gp41 - one in a "native" state as it might be found on a resting virion. The other in a "fusogenic" state to reflect

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conformational changes triggered following binding of gp120 to CD4 and just prior to fusion with the target cell membrane. The strong binding affinity between gp120 and CD4 may actually represent the trigger for the fusion process obviating the need for a pH change
5 such as occurs for viruses that fuse within intracellular vesicles. The two major features of both models are: (1) the leucine zipper sequences (DP107) in each chain of oligomeric envelope are held apart in the native state and are only allowed access
10 to one another in the fusogenic state so as to form the extremely stable coiled-coils, and (2) association of the DP178 and DP107 sites as they exist in gp41 occur either in the native or fusogenic state. FIG. 11A depicts DP178/DP107 interaction in the native
15 state as a molecular class. On the other hand, if one assumes that the most stable form of the envelope occurs in the fusogenic state, the model in FIG. 11B can be considered.

When synthesized as peptides, both DP107 and
20 DP178 are potent inhibitors of HIV infection and fusion, probably by virtue of their ability to form complexes with viral gp41 and interfere with its fusogenic process; e.g., during the structural transition of the viral protein from the native
25 structure to the fusogenic state, the DP178 and DP107 peptides may gain access to their respective binding sites on the viral gp41, and exert a disruptive influence. DP107 peptides which demonstrate anti-HIV activity are described in Applicants' co-pending
30 application Serial No. 07/927,532, filed August 7, 1992, which is incorporated by reference herein in its entirety.

As shown in the working examples, infra, a truncated recombinant gp41 protein corresponding the
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ectodomain of gp41 containing both DP107 and DP178 domains (excluding the fusion peptide, transmembrane region and cytoplasmic domain of gp41) did not inhibit HIV-1 induced fusion. However, when a single mutation was introduced to disrupt the coiled-coil structure of the DP107 domain -- a mutation which results in a total loss of biological activity of DP107 peptides -- the inactive recombinant protein was transformed to an active inhibitor of HIV-1 induced fusion. This transformation may result from liberation of the potent DP178 domain from a molecular clasp with the leucine zipper, DP107 domain.

For clarity of discussion, the invention will be described for DP178 peptide inhibitors of HIV. However, the principles may be analogously applied to other fusogenic enveloped viruses, including but not limited to those viruses containing the peptides listed in Tables V through X, below.

5.1. DP-178 AND DP-178-LIKE PEPTIDES

The peptide DP-178 (SEQ ID:1) of the invention corresponds to amino acid residues 638 to 673 of the transmembrane protein gp41 from the HIV-1_{LAI} isolate, and has the 36 amino acid sequence (reading from amino to carboxy terminus):

NH₂-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-COOH (SEQ ID:1)

In addition to the full-length DP-178 (SEQ ID:1) 36-mer, the peptides of the invention may include truncations of the DP-178 (SEQ ID:1) peptide which exhibit antiviral activity. Such truncated DP-178 (SEQ ID:1) peptides may comprise peptides of between 3 and 36 amino acid residues (*i.e.*, peptides ranging in size from a tripeptide to a 36-mer polypeptide), and

may include but are not limited to those listed in Tables I and II, below. Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group ($-NH_2$) and "Z" may represent a carboxyl ($-COOH$) group.

- 5 Alternatively, as described below, "X" and/or "Z" may represent a hydrophobic group, an acetyl group, a FMOC group, an amido group, or a covalently attached macromolecule.

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TABLE I
DP-178 (SEQ ID:1) CARBOXY TRUNCATIONS

X-YTS-Z
 X-YTSL-Z
 X-YTSLI-Z
 X-YTSLIH-Z
 5 X-YTSLIHS-Z
 X-YTSLIHSL-Z
 X-YTSLIHSLI-Z
 X-YTSLIHSLIE-Z
 X-YTSLIHSLIEE-Z
 X-YTSLIHSLIEES-Z
 X-YTSLIHSLIEESQ-Z
 10 X-YTSLIHSLIEESQN-Z
 X-YTSLIHSLIEESQNNQ-Z
 X-YTSLIHSLIEESQNNQQ-Z
 X-YTSLIHSLIEESQNNQQE-Z
 X-YTSLIHSLIEESQNNQQEK-Z
 X-YTSLIHSLIEESQNNQQEKN-Z
 X-YTSLIHSLIEESQNNQQEKNE-Z
 X-YTSLIHSLIEESQNNQQEKNEQ-Z
 15 X-YTSLIHSLIEESQNNQQEKNEQE-Z
 X-YTSLIHSLIEESQNNQQEKNEQEL-Z
 X-YTSLIHSLIEESQNNQQEKNEQELL-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLE-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLEL-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELD-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDK-Z
 20 X-YTSLIHSLIEESQNNQQEKNEQELLELDKW-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWA-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWAS-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLW-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWN-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWNW-Z
 25 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWNWF-Z

The one letter amino acid code is used.

Additionally,

"X" may represent an amino group, a hydrophobic group,
 including but not limited to carbobenzoxyl, dansyl, or
 30 T-butyloxycarbonyl; an acetyl group; a 9-
 fluorenylmethoxy-carbonyl (FMOC) group; a
 macromolecular carrier group including but not limited
 to lipid-fatty acid conjugates, polyethylene glycol,
 or carbohydrates.

"Z" may represent a carboxyl group; an amido group; a
 T-butyloxycarbonyl group; a macromolecular carrier
 35 group including but not limited to lipid-fatty acid
 conjugates, polyethylene glycol, or carbohydrates.

TABLE II
DP-178 (SEQ ID:1) AMINO TRUNCATIONS

	X-NWF-Z
	X-WNWF-Z
	X-LWNWF-Z
	X-SLWNWF-Z
5	X-ASLWNWF-Z
	X-WASLWNWF-Z
	X-KWASLWNWF-Z
	X-DKWASLWNWF-Z
	X-LDKWASLWNWF-Z
	X-ELDKWASLWNWF-Z
	X-LELDKWASLWNWF-Z
10	X-LLELDKWASLWNWF-Z
	X-ELLELDKWASLWNWF-Z
	X-QELLELDKWASLWNWF-Z
	X-EQELLELDKWASLWNWF-Z
	X-NEQELLELDKWASLWNWF-Z
	X-KNEQELLELDKWASLWNWF-Z
	X-EKNEQELLELDKWASLWNWF-Z
	X-QEKNEQELLELDKWASLWNWF-Z
15	X-QQEKNEQELLELDKWASLWNWF-Z
	X-NQQEKNEQELLELDKWASLWNWF-Z
	X-QNQEKNEQELLELDKWASLWNWF-Z
	X-SQNQQEKNEQELLELDKWASLWNWF-Z
	X-ESQNQQEKNEQELLELDKWASLWNWF-Z
	X-EESQNQQEKNEQELLELDKWASLWNWF-Z
	X-IEESQNQQEKNEQELLELDKWASLWNWF-Z
20	X-LIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-SLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-HSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-IHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
25	X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z

The one letter amino acid code is used.

Additionally,

"X" may represent an amino group, a hydrophobic group, including but not limited to carbobenzoxyl, dansyl, or T-butyloxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

"Z" may represent a carboxyl group; an amido group; a T-butyloxycarbonyl group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

The antiviral peptides of the invention also include analogs of DP-178 and/or DP-178 truncations which may include, but are not limited to, peptides comprising the DP-178 (SEQ ID:1) sequence, or DP-178 truncated sequence, containing one or more amino acid
5 substitutions, insertions and/or deletions. Analogs of DP-178 homologs, described below, are also within the scope of the invention. The DP-178 analogs of the invention exhibit antiviral activity, and may, further, possess additional advantageous features,
10 such as, for example, increased bioavailability, and/or stability, or reduced host immune recognition.

HIV-1 and HIV-2 envelope proteins are structurally distinct, but there exists a striking amino acid conservation within the DP-178-
15 corresponding regions of HIV-1 and HIV-2. The amino acid conservation is of a periodic nature, suggesting some conservation of structure and/or function. Therefore, one possible class of amino acid substitutions would include those amino acid changes
20 which are predicted to stabilize the structure of the DP-178 peptides of the invention.

Amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions consist of replacing one or more amino
25 acids of the DP-178 (SEQ ID:1) peptide sequence with amino acids of similar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to aspartic acid (D) amino acid substitution. When only conserved substitutions are
30 made, the resulting peptide is functionally equivalent to DP-178 (SEQ ID:1) or the DP-178 peptide from which it is derived. Non-conserved substitutions consist of replacing one or more amino acids of the DP-178 (SEQ
ID:1) peptide sequence with amino acids possessing
35 dissimilar charge, size, and/or hydrophobicity

characteristics, such as, for example, a glutamic acid (E) to valine (V) substitution.

Amino acid insertions may consist of single amino acid residues or stretches of residues ranging from 2 to 15 amino acids in length. One or more insertions
5 may be introduced into DP-178 (SEQ ID:1), DP-178 fragments, analogs and/or DP-178 homologs (described below).

Deletions of DP-178 (SEQ ID:1), DP-178 fragments, analogs, and/or DP-178 homologs (described below) are
10 also within the scope of the invention. Such deletions consist of the removal of one or more amino acids from the DP-178 or DP-178-like peptide sequence, with the lower limit length of the resulting peptide sequence being 4 to 6 amino acids. Such deletions may
15 involve a single contiguous or greater than one discrete portion of the peptide sequences.

The peptides of the invention may further include homologs of DP-178 (SEQ ID:1) and/or DP-178 truncations which exhibit antiviral activity. Such
20 DP-178 homologs are peptides whose amino acid sequences are comprised of the amino acid sequences of peptide regions of other (*i.e.*, other than HIV-1_{LA1}) viruses that correspond to the gp41 peptide region from which DP-178 (SEQ ID:1) was derived. Such
25 viruses may include, but are not limited to, other HIV-1 isolates and HIV-2 isolates. DP-178 homologs derived from the corresponding gp41 peptide region of other (*i.e.*, non HIV-1_{LA1}) HIV-1 isolates may include, for example, peptide sequences as shown below.

30

NH₂-YTNTIYTLLEESQNQQEKNEQEELLELDKWASLWNWF-COOH (DP-185; SEQ ID:3);

35

NH₂-YTGIIYNLLEESQNQQEKNEQEELLELDKWANLWNWF-COOH (SEQ ID:4);

NH₂-YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF-COOH (SEQ ID:5).

SEQ ID:3 (DP-185), SEQ ID:4, and SEQ ID:5 are derived from HIV-1_{SP2}, HIV-1_{RF}, and HIV-1_{MN} isolates, respectively. Underlined amino acid residues refer to those residues that differ from the corresponding position in the DP-178 (SEQ ID:1) peptide. One such DP-178 homolog, DP-185 (SEQ ID:3), is described in the Working Example presented in Section 6, below, where it is demonstrated that DP-185 (SEQ ID:3) exhibits antiviral activity. The DP-178 homologs of the invention may also include truncations, amino acid substitutions, insertions, and/or deletions, as described above.

In addition, striking similarities, as shown in FIG. 1, exist within the regions of HIV-1 and HIV-2 isolates which correspond to the DP-178 sequence. A DP-178 homolog derived from the HIV-2_{NH2} isolate has the 36 amino acid sequence (reading from amino to carboxy terminus):

NH₂-LEANISQSLEQAQIQQEKNMVELQKLNSWDVFTNWL-COOH (SEQ ID:7)

Table III and Table IV show some possible truncations of the HIV-2_{NH2} DP-178 homolog, which may comprise peptides of between 3 and 36 amino acid residues (*i.e.*, peptides ranging in size from a tripeptide to a 36-mer polypeptide). Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group (-NH₂) and "Z" may represent a carboxyl (-COOH) group. Alternatively, as described below, "X" and/or "Z" may represent a hydrophobic group, an acetyl group, a FMOC group, an amido group, or a covalently attached macromolecule, as described below.

TABLE III

HIV-2_{NIH} DP-178 homolog carboxy truncations.

X-LEA-Z
 X-LEAN-Z
 X-LEANI-Z
 X-LEANIS-Z
 5 X-LEANISQ-Z
 X-LEANISQS-Z
 X-LEANISQSL-Z
 X-LEANISQSLE-Z
 X-LEANISQSLEQ-Z
 X-LEANISQSLEQA-Z
 X-LEANISQSLEQAQ-Z
 10 X-LEANISQSLEQAQI-Z
 X-LEANISQSLEQAQIQ-Z
 X-LEANISQSLEQAQIQQ-Z
 X-LEANISQSLEQAQIQQE-Z
 X-LEANISQSLEQAQIQQEK-Z
 X-LEANISQSLEQAQIQQEKN-Z
 X-LEANISQSLEQAQIQQEKNM-Z
 X-LEANISQSLEQAQIQQEKNMY-Z
 15 X-LEANISQSLEQAQIQQEKNMYE-Z
 X-LEANISQSLEQAQIQQEKNMYEL-Z
 X-LEANISQSLEQAQIQQEKNMYELQ-Z
 X-LEANISQSLEQAQIQQEKNMYELQK-Z
 X-LEANISQSLEQAQIQQEKNMYELQKL-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLN-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNS-Z
 20 X-LEANISQSLEQAQIQQEKNMYELQKLNSW-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWD-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDV-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVF-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFT-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTN-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNW-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z

25 The one letter amino acid code is used.

Additionally,

"X" may represent an amino group, a hydrophobic group,
 including but not limited to carbobenzoxyl, dansyl, or
 30 T-butyloxycarbonyl; an acetyl group; a 9-
 fluorenylmethoxy-carbonyl (Fmoc) group; a
 macromolecular carrier group including but not limited
 to lipid-fatty acid conjugates, polyethylene glycol,
 or carbohydrates.

"Z" may represent a carboxyl group; an amido group; a
 T-butyloxycarbonyl group; a macromolecular carrier
 35 group including but not limited to lipid-fatty acid
 conjugates, polyethylene glycol, or carbohydrates.

TABLE IV

HIV-2_{NDZ} DP-178 homolog amino truncations.

	X-NWL-Z
	X-TNWL-Z
	X-FTNWL-Z
	X-VFTNWL-Z
5	X-DVFTNWL-Z
	X-WDVFTNWL-Z
	X-SWDVFTNWL-Z
	X-NSWDVFTNWL-Z
	X-LNSWDVFTNWL-Z
	X-KLNSWDVFTNWL-Z
	X-QKLNSWDVFTNWL-Z
10	X-LQKLNSWDVFTNWL-Z
	X-ELQKLNSWDVFTNWL-Z
	X-YELQKLNSWDVFTNWL-Z
	X-MYELQKLNSWDVFTNWL-Z
	X-NMYELQKLNSWDVFTNWL-Z
	X-KNMYELQKLNSWDVFTNWL-Z
	X-EKNMYELQKLNSWDVFTNWL-Z
	X-QEKNMYELQKLNSWDVFTNWL-Z
15	X-QQEKNMYELQKLNSWDVFTNWL-Z
	X-IQQEKNMYELQKLNSWDVFTNWL-Z
	X-QIQQEKNMYELQKLNSWDVFTNWL-Z
	X-AQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-QAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-EQAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-LEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
20	X-SLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-QSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-SQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-ISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-NISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-ANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-EANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
25	X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z

The one letter amino acid code is used.

Additionally,

"X" may represent an amino group, a hydrophobic group, including but not limited to carbobenzoxyl, dansyl, or T-butyloxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (Fmoc) group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

"Z" may represent a carboxyl group; an amido group; a T-butyloxycarbonyl group; a macromolecular carrier group including but not limited to lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates.

5.2. DP-107 and DP-178 ANALOGOUS ANTIVIRAL PEPTIDES

Peptid sequences functionally corresponding, and thus analogous to, the DP-178 sequences of the invention, described, above, in Section 5.1 may be found in other, non-HIV-1 envelope viruses. Further, peptide sequences functionally corresponding, and thus analogous to, DP-107, an HIV-1-derived antiviral peptide, may also be found in other, non-HIV-1 envelope viruses. DP-107 is a 38 amino acid peptide corresponding to residues 558 to 595 of HIV-1_{LA1} transmembrane (TM) gp41 protein, which exhibits potent anti-viral activity. DP-107 is more fully described in Applicant's co-pending U.S. Patent Application Ser. No. 07/927,532. These DP-107-like and DP-178-like analogous peptides and present in TM proteins of envelope viruses and preferably exhibit antiviral activity, most preferably antiviral activity which is specific to the virus in which their native sequences are found.

DP-107-like and DP-178-like peptides may be identified, for example, by utilizing a computer-assisted search strategy such as that described and demonstrated, below, in the Examples presented in Sections 9 through 16. The search strategy identifies regions in other viruses that are similar in predicted secondary structure to DP-107 and DP-178.

This search strategy is described fully, below, in the Example presented in Section 9. While this search strategy is based, in part, on a primary amino acid motif deduced from DP-107 and DP-178, it is not based solely on searching for primary amino acid sequence homologies, as such protein sequence homologies exist within, but not between major groups of viruses. For example, primary amino acid sequence homology is high within the TM protein of different

strains of HIV-1 or within the TM protein of different isolates of simian immunodeficiency virus (SIV).

Primary amino acid sequence homology between HIV-1 and SIV, however, is low enough so as not to be useful.

It is not possible, therefore, to find DP-107 or DP-
5 178-like peptides within other viruses, whether structurally, or otherwise, based on primary sequence homology, alone.

Further, while it would be potentially useful to identify primary sequence arrangements of amino acids
10 based on the physical chemical characteristics of different classes of amino acids rather than based on the specific amino acids themselves, for instance, a by concentrating on the coiled-coil nature of the peptide sequence, a computer algorithm designed by
15 Lupas et al. to identify such coiled-coil propensities of regions within proteins (Lupas, A., et al., 1991 Science 252:1162-1164) is inadequate for identifying protein regions analogous to DP-107 or DP-178.

Specifically, analysis of HIV-1 gp160 (containing
20 both gp120 and gp41) using the Lupas algorithm does not identify the coiled-coil region within DP-107. It does, however, identify a region within DP-178 beginning eight amino acids N-terminal to the start of DP-178 and ending eight amino acids from the C-
25 terminus. The DP-107 peptide has been shown experimentally to form a stable coiled coil. A search based on the Lupas search algorithm, therefore, would not have identified the DP-107 coiled-coil region. Conversely, the Lupas algorithm identified the DP-178
30 region as a potential coiled-coil motif. However, the peptide DP-178 derived from this region failed to form a coiled coil in solution. A possible explanation for the inability of the Lupas search algorithm to accurately identify coiled-coil sequences within the
35 HIV-1 TM, is that the Lupas algorithm is based on the

structure of coiled c ils from proteins that are not structurally or functionally similar to the TM proteins of viruses, antiviral peptides (e.g. DP-107 and DP-178) of which are an object of this invention.

5 The computer search strategy of the invention, as demonstrated in the Examples presented below, in Sections 9 through 16, successfully identifies regions of viral TM proteins similar to DP-107 or DP-178. This search strategy was designed to be used with a commercially-available sequence database packages,
10 preferably PC/Gene. A series of motifs were designed and engineered to range in stringency from very strict to very broad, as discussed in Section 9.

Among the protein sequence seach motifs which may be utilized in such a computer-assisted DP-107-like
15 and DP-178-like antiviral peptide search are the 107x178x4 motif, the ALLMOTI5 motif, and the PLZIP series of motifs, each of which is described in the Example presented in Section 9, below, with 107x178x4 being preferred.

20 Coiled-coiled sequences are thought to consist of heptad amino acid repeats. For ease of description, the amino acid positions within the heptad repeats are sometimes referred to as A through G, with the first position being A, the second B, etc. The motifs used
25 to identify DP-107-like and DP-178-like sequences herein are desined to specifically search for and identify such heptad repeats. In the descriptions of each of the motifs described, below, amino acids enclosed by brackets , i.e., [], designate the only
30 amino acid residues that are acceptable at the given position, while amino acids enclosed by braces, i.e., {}, designate the only amino acids which are unacceptable at the given heptad position. When a set of bracketed or braced amino acids is followed by a
35 number in parentheses i.e., (), it refers to the

number of subsequent amino acid positions for which the designated set of amino acids hold, e.g., a (2) means "for the next two heptad amino acid positions."

The ALLMOTI5 is written as follows:

5 {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
 {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
 {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
 {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
 {CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-

Translating this motif, it would read: "at the first (A) position of the heptad, any amino acid residue except C, D, G, H, or P is acceptable, at the next two (B,C) amino acid positions, any amino acid residue except C, F, or P is acceptable, at the fourth heptad position (D), any amino acid residue except C, D, G, H, or P is acceptable, at the next three (E, F, G) amino acid positions, any amino acid residue except C, F, or P is acceptable. This motif is designed to search for five consecutive heptad repeats (thus the repeat of the first line five times), meaning that it searches for 35-mer sized peptides. It may also be designed to search for 28-mers, by only repeating the initial motif four times. With respect to the ALLMOTI5 motif, a 35-mer search is preferred. Those viral sequences identified via such an ALLMOTI5 motif are listed in Table V, below, at the end of this Section. The viral sequences listed in Table V potentially exhibit antiviral activity, may be useful in the identification of antiviral compounds, and are intended to be within the scope of the invention.

The 107x178x4 motif is written as follows:

30 [EIKLNQSTVWY]-{CFMP}(2)-[EIKLNQSTVWY]-{CFMP}(3)-
 [EIKLNQSTVWY]-{CFMP}(2)-[EIKLNQSTVWY]-{CFMP}(3)-
 [EIKLNQSTVWY]-{CFMP}(2)-[EIKLNQSTVWY]-{CFMP}(3)-
 [EIKLNQSTVWY]-{CFMP}(2)-[EIKLNQSTVWY]-{CFMP}(3)-

Translating this motif, it would read: "at the first (A) position of the heptad, any amino acid residue except E, F, I, K, L, N, Q, S, T, V, W, or Y

is acceptable, at the next two (B,C) amino acid positions, any amino acid residue except C, F, M or P is acceptable, at the fourth position (D), any amino acid residue except E, F, I, K, L, N, Q, S, T, V, W, or Y is acceptable, at the next three (E, F, G) amino acid positions, any amino acid residue except C, F, M or P is acceptable. This motif is designed to search for four consecutive heptad repeats (thus the repeat of the first line four times), meaning that it searches for 28-mer sized peptides. It may also be designed to search for 35-mers, by repeating the initial motif five times. With respect to the 107x178x4 motif, a 28-mer search is preferred. Those viral sequences identified via such a 107x178x4 motif are listed in Table V, below, at the end of this Section. The viral sequences listed in Table V potentially exhibit antiviral activity, may be useful in the identification of antiviral compounds, and are intended to be within the scope of the invention.

The PLZIP series of motifs are as listed in FIG. 19. These motifs are designed to identify leucine zipper coiled-coil like heptads wherein at least one proline residue is present at some predefined distance N-terminal to the repeat. These PLZIP motifs find regions of proteins with similarities to HIV-1 DP-178 generally located just N-terminal to the transmembrane anchor. These motifs may be translated according to the same convention described above. Each line depicted in FIG. 19 represents a single, complete search motif. "X" in these motifs refers to any amino acid residue. In instances wherein a motif contains two numbers within parentheses, this refers to a variable number of amino acid residues. For example, X (1,12) is translated to "the next one to twelve amino acid residues, inclusive, may be any amino acid".

Tables VI through X, below, at the end of this

Section, list hits from such PLZIP motifs. The viral sequences listed in Table VI through X potentially exhibit antiviral activity, may be useful in the identification of antiviral compounds, and are intended to be within the scope of the invention.

5 The Examples presented in Sections 17 and 18, below, demonstrate that respiratory syncytial virus and parainfluenza virus sequences identified via such a computer search exhibit antiviral and/or structural characteristics similar to those of DP-107 or DP-178.

10 The DP-107-like and DP-178-like analogous peptides may, further, contain any of the additional groups described for DP-178, above, in Section 5.1. For example, these peptides may include any of the additional amino-terminal groups which "X" of Tables I
15 through IV may represent, and may also include any of the carboxy-terminal groups which "Z" of Tables I through IV may represent.

 Additionally, such DP-107-like and DP-178-like peptides may further include DP-107-like or DP-178-like
20 peptides, such as those listed in Tables V through X, above, containing one or more amino acid substitutions, insertions, and/or deletions. Also, analogs of such DP-107-like and DP-178-like peptides are intended to be within the scope of the invention.
25 Such analogs of the invention may exhibit increased antiviral activity, and may, further, possess increased bioavailability, and/or stability, or reduced immune recognition.

 The DP-107-like and DP-178-like amino acid
30 substitutions, insertions and deletions, are as described for DP-178, above, in Section 5.1. Analog modifications are as described, below, in Section 5.3.

35

TABLE V

**Search Results Summary for 107x178x4 and
ALLMOTI5 Motifs**

[illegible]

PENV HV1H3	646-894	631-883	781-818	PENV HV1B1	501-580	608-708	783-831
PENV HV1J3	568-806	642-884	802-829	PENV HV1B1	510-589	618-717	772-841
PENV HV1J3		622-876	783-811	PENV HV1C4	510-589	628-724	778-866
PENV HV1K8	555-586	637-877	776-824	PENV HV1E1	502-581	607-709	768-828
PENV HV1M1	647-686	633-707	784-828	PENV HV1H2	508-584	610-712	767-838
PENV HV1M1	643-582	628-881	788-818	PENV HV1H3	505-584	610-712	767-843
PENV HV1M1	667-686	632-884	791-819	PENV HV1J3	517-608	622-723	778-843
PENV HV1M1	558-583	621-873	783-813	PENV HV1J3	497-588	603-704	758-835
PENV HV1M1	644-883	630-704	786-820	PENV HV1K8	511-546	655-699	818-718
PENV HV1M1	545-584	631-883	781-818	PENV HV1M1	507-588	617-714	770-825
PENV HV1M1	864-602	640-682	800-832	PENV HV1M1	503-582	622-710	768-841
PENV HV1M1	836-585	622-874	782-809	PENV HV1M1	508-585	617-713	774-841
PENV HV1M1	841-688	627-879	787-815	PENV HV1M1	498-584	601-702	767-825
PENV HV1M1	645-693	631-883		PENV HV1M1	487-583	610-711	768-842
PENV HV1M1	545-593	631-883	781-818	PENV HV1M1	508-584	610-712	767-843
PENV HV1M1	836-584	622-874	782-809	PENV HV1M1	507-603	618-721	776-862
PENV HV1M1	842-581	628-880	780-820	PENV HV1M1	498-586	602-703	758-830
PENV HV1M1	648-583	630-682	782-822	PENV HV1M1	484-580	607-708	783-837
PENV HV1M1	675-601	634-678	787-828	PENV HV1M1	498-584	611-712	787-834
PENV HV1M1	645-584	627-888	781-823	PENV HV1M1	498-584	611-712	787-836
PENV HV1M1	632-591	621-848	663-897	PENV HV1M1	488-584	602-703	758-827
PENV HV1M1	634-583	623-880	655-898	PENV HV1M1	602-581	607-709	784-831
PENV HV1M1	623-880	655-582	644-898	PENV HV1M1	504-583	608-711	786-840
PENV HV1M1	624-581	556-583	613-640	PENV HV1M1	512-601	617-875	682-718
PENV HV1M1	624-581	556-583	613-640	PENV HV1M1	522-584	612-712	777-839
PENV HV1M1	633-582	622-888		PENV HV1M1	510-585	617-880	
PENV HV1M1	627-884	558-588	648-882	PENV HV1M1	512-597	618-708	
PENV HV1M1	557-584	614-673		PENV HV1M1	501-586	608-898	
PENV HV1M1	527-584	558-588	648-882	PENV HV1M1	502-587	608-898	
PENV HV1M1	473-512			PENV HV1M1	488-587	608-898	
PENV HV1M1	488-516			PENV HV1M1	511-586	618-708	
PENV HV1M1	517-544			PENV HV1M1	505-580	612-702	
PENV HV1M1	510-539			PENV HV1M1	520-588	614-700	
PENV HV1M1	523-583			PENV HV1M1	505-580	612-702	
PENV HV1M1	523-583			PENV HV1M1	387-422	486-827	
PENV HV1M1	523-583			PENV HV1M1	403-456	571-805	
PENV HV1M1	510-640			PENV HV1M1	473-828	537-571	
PENV HV1M1	40-81			PENV HV1M1	474-628	538-572	
PENV HV1M1	502-543			PENV HV1M1	503-586	587-601	
PENV HV1M1	487-538			PENV HV1M1	498-580	582-596	
PENV HV1M1	497-538			PENV HV1M1	520-584	578-810	
PENV HV1M1	468-486	582-588		PENV HV1M1	520-584	578-810	
PENV HV1M1	468-486	582-588		PENV HV1M1	520-584	578-810	
PENV HV1M1	422-470			PENV HV1M1	504-551	563-587	
PENV HV1M1	57-84			PENV HV1M1	40-82	104-136	
PENV HV1M1	42-68	190-223	780-807	PENV HV1M1	502-554	588-600	
PENV HV1M1	487-517			PENV HV1M1	487-548	591-595	

PENV 8FV1	14-41	868-801				PENV MLVRK	497-549	581-586					
PENV 8FV3L	18-45	318-357	673-700	863-888		PENV MMTVB	477-539	558-612					
PENV 8IV1	581-588	582-619	652-678	687-724		PENV MMTVG	477-539	558-612					
PENV 8IVAQ	588-593	587-624	688-685	703-730		PENV MPNV	408-474						
PENV 8IVAI	548-603	634-708				PENV MSVFB	43-98	107-141					
PENV 8IVAT	580-617	661-678				PENV QMVVB	22-84	185-223	684-748	780-816			
PENV 8IVCZ	528-584	627-664				PENV RMCV	484-528	540-574					
PENV 8IVGB	588-650	784-816				PENV RGVV	342-378						
PENV 8IVM1	550-609	671-715				PENV 8FV1	1-41	101-140	164-206	321-365	563-561	668-804	
PENV 8IVM2	185-215	277-289				PENV 8FV3L	5-46	159-208	318-357	680-708	883-901		
PENV 8IVMK	583-608					PENV 8IV1	289-310	581-623	643-683				
PENV 8IVML	548-608					PENV 8IVAG	556-628	651-689	808-852				
PENV 8IV84	583-612	642-669	691-718			PENV 8IVAT	287-291	338-370	538-587	782-840			
PENV 8IV8P	584-595	646-722				PENV 8IVAT	204-288	548-621	644-692	786-833			
PENV 8IVRH	400-462					PENV 8IVCZ	263-291	330-366	612-684	889-703	803-837		
PENV 8RV1	408-471					PENV 8IVGB	588-654	677-725					
PENV 8RV1	773-800					PENV 8IVM1	114-181	486-508	528-613	635-725	809-864		
PENV 8RV1	780-807					PENV 8IVM2	71-116	134-218	245-331				
PENV 8RV2	782-809					PENV 8IVMK	484-505	540-612	638-724				
PHEMA CVBLY	208-242					PENV 8IVML	484-505	540-612	638-724				
PHEMA CVBM	208-242					PENV 8IV84	486-508	517-618	638-728	812-853			
PHEMA CVBQ	388-428					PENV 8IV8P	476-613	521-620	642-732	811-848			
PHEMA CVHOC	208-242					PENV 8IVRH	400-488						
PHEMA IAIC	387-453					PENV 8RV1	408-475						
PHEMA IABAN	371-437					PENV 8RV1	21-82	184-222	637-740	773-808			
PHEMA IABUD	381-451					PENV 8RV1	21-82	184-222	643-748	780-816			
PHEMA IACKA	381-451					PENV 8RV2	21-82	184-222	648-748	782-818			
PHEMA IACKG	382-441	484-528				PHEMA CVBLY	208-242						
PHEMA IACKP	388-428					PHEMA CVBM	208-242						
PHEMA IACKG	388-428					PHEMA CVBQ	208-242						
PHEMA IACKV	384-443					PHEMA CVHOC	208-242						
PHEMA IADA1	381-451					PHEMA IAIC	380-458						
PHEMA IADA2	423-453	488-543				PHEMA IABAN	384-440						
PHEMA IADA3	387-453					PHEMA IABUD	378-454						
PHEMA IADA4	418-478					PHEMA IACKA	378-454						
PHEMA IADC2	381-451					PHEMA IACKG	108-142	376-475	494-528				
PHEMA IADH1	402-453	508-533				PHEMA IACKP	380-452	487-532					
PHEMA IADH2	371-437					PHEMA IACKQ	380-452	487-532					
PHEMA IADH3	371-437					PHEMA IACKS	377-469	504-549					
PHEMA IADH4	371-437					PHEMA IACKV	112-148	377-469					
PHEMA IADH5	371-437					PHEMA IADA1	377-454						
PHEMA IADH6	371-437					PHEMA IADA2	377-478	495-547					
PHEMA IADH7	371-437					PHEMA IADA3	380-453						
PHEMA IADIR	418-445					PHEMA IADA4	378-478	508-548					
PHEMA IADH2	387-453					PHEMA IADC2	378-454						
PHEMA IADH2	381-451					PHEMA IADE1	21-55	377-472					
PHEMA IADH2	381-451					PHEMA IADH1	384-440						

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PHEMA IATKR	381-422									PHEMA IAMEG	394-440						
PHEMA IATKW	419-449	600-636								PHEMA IAMIN	108-142	375-476					
PHEMA IAUDO	387-453									PHEMA IANTG	380-466						
PHEMA IAUBS	426-478									PHEMA IAPIL	378-477	480-534					
PHEMA IAVI7	388-484									PHEMA IAPUE	378-478	608-648					
PHEMA IAWIL	424-477									PHEMA IARUD	378-484						
PHEMA IAZCO	387-453									PHEMA IABE2	378-484						
PHEMA IAZH2	371-437									PHEMA IABH2	378-474	500-562					
PHEMA IAZH3	371-437									PHEMA IABTA	112-148	377-469					
PHEMA IAZNJ	418-478	608-647								PHEMA IATKI	378-471	608-661					
PHEMA IAZUK	387-483									PHEMA IATKM	378-484						
PHEMA INBBE	400-431	439-463								PHEMA IATKO	392-470	504-648					
PHEMA INBBO	380-421	428-473								PHEMA IATKP	378-484	483-640					
PHEMA INBEN	388-428	437-481								PHEMA IATKR	30-84	374-474					
PHEMA INBNK	381-418	428-473								PHEMA IATKW	373-472	487-639					
PHEMA INBLE	388-430	438-482								PHEMA IATRA	21-56						
PHEMA INBMD	388-420	428-472								PHEMA IAUDO	387-469						
PHEMA INBME	383-424	432-476								PHEMA IAUBS	378-478	608-648					
PHEMA INBOR	388-429	437-481								PHEMA IAVI7	381-467						
PHEMA INBSJ	388-428	437-481								PHEMA IAWIL	376-477	606-647					
PHEMA INBUS	381-422	430-474								PHEMA IAZCO	380-468						
PHEMA INBVI	383-424	432-476								PHEMA IAZH2	384-440						
PHEMA INBVK	400-431	438-483								PHEMA IAZH3	384-440						
PHEMA INCCA	488-671									PHEMA IAZIN	378-478	608-648					
PHEMA INCN	483-669									PHEMA IAZIJ	378-478	608-648					
PHEMA NCGL	483-669									PHEMA IAZUK	380-468						
PHEMA NCHY	482-668									PHEMA INBBE	388-473						
PHEMA NCJH	488-672									PHEMA INBBO	378-483						
PHEMA NCKY	482-668									PHEMA INBEN	380-471						
PHEMA NCMI	482-668									PHEMA INBNK	381-463						
PHEMA NCNA	482-668									PHEMA INBLE	387-472						
PHEMA INCP1	483-669									PHEMA INBMD	377-482						
PHEMA INCF2	483-669									PHEMA INBME	381-469						
PHEMA INCF3	483-669									PHEMA INBOR	380-471						
PHEMA INCTA	483-669									PHEMA INBSJ	380-471						
PHEMA NCYA	483-669									PHEMA INBUS	378-484						
PHEMA NDVA	64-81									PHEMA INBVI	381-468						
PHEMA NDVB	64-81									PHEMA INBVK	389-473						
PHEMA NDVO	64-81									PHEMA INCCA	483-671						
PHEMA NDVH	64-81									PHEMA INCN	471-669						
PHEMA NDVI	64-81									PHEMA INCGL	471-669						
PHEMA NDVM	64-81									PHEMA INCHY	470-668						
PHEMA NDVQ	64-81									PHEMA INCJH	484-672						
PHEMA NDVTG	64-81									PHEMA INCKY	470-668						
PHEMA NDVU	64-81									PHEMA INCOMI	470-668						
PHEMA PHODV	39-68	40-73								PHEMA INCNA	470-668						
										PHEMA INCP1	471-669						

PHEMA PI1HW	70-110	300-303				PHEMA INCP2	471-559
PHEMA PI3B	80-93					PHEMA INCP3	471-559
PHEMA PI3H4	27-61					PHEMA INCTA	471-559
PHEMA PI3HA	27-61					PHEMA INCTA	471-559
PHEMA PI3HT	27-76					PHEMA MEABE	40-80
PHEMA PI3HU	23-70					PHEMA MEABH	40-80
PHEMA PI3HV	27-61					PHEMA MEABH	40-87
PHEMA PI3HW	27-61					PHEMA MEABY	40-87
PHEMA PI3HX	27-61					PHEMA MUMPM	34-99
PHEMA RACV1	100-214					PHEMA MUMPR	34-99
PHEMA 8END6	70-108	250-263				PHEMA MUMPS	34-99
PHEMA 8ENDF	70-108					PHEMA NDVA	8-52
PHEMA 8ENDH	70-108					PHEMA NDVB	1-49
PHEMA 8ENDJ	70-108					PHEMA NDVD	1-49
PHEMA 8ENDZ	70-108					PHEMA NDVM	1-49
PHEMA 6VA1	22-82	304-421				PHEMA NDVQ	1-49
PHEMA VACCC	118-148	176-202	210-243			PHEMA NDVTG	1-49
PHEMA VACCI	108-148	176-202	210-243			PHEMA NDVU	1-49
PHEMA VACCT	118-148	176-202	210-243			PHEMA PHODV	30-73
PHEMA VACCV	108-148	176-202	210-243			PHEMA PI1HW	60-110
PVENV DHV11	318-366					PHEMA PI2H	247-281
PVENV EAV	120-147					PHEMA PI2HT	247-281
PVENV THOGV	313-347					PHEMA PI3B	30-83
PVF03 VACCC	71-110	186-212				PHEMA PI3HA	13-110
PVF03 VACCV	71-110	186-212				PHEMA PI3HA	20-110
PVF05 VACCP	33-60					PHEMA PI3HT	13-110
PVF08 VACCV	33-60					PHEMA PI3HU	13-110
PVF11 VACCC	270-317					PHEMA PI3HV	13-110
PVF12 VACCC	10-37	113-140	554-581			PHEMA PI3HW	13-110
PVF12 VACCP	10-37	113-140	554-581			PHEMA PI3HX	13-110
PVF16 VACCC	35-62	162-179				PHEMA PI4HA	84-88
PVF16 VACCP	35-62	162-179				PHEMA RACV1	100-214
PVF16 VACCV	35-62					PHEMA RINDK	40-87
PVF4 FOWPV	146-173					PHEMA RINDL	40-87
PVFUS ORFRZ	50-88					PHEMA 8ENDB	67-110
PVFUS VACCC	37-64					PHEMA 8ENDF	67-110
PVFUS VACCV	37-64					PHEMA 8ENDH	67-110
PVG01 VACCC	228-262	301-335				PHEMA 8ENDJ	67-110
PVG01 VACCV	104-191	240-274				PHEMA 8ENDZ	87-110
PVG01 VARV	225-262	301-335				PHEMA 6VA1	10-52
PVG02 VACCV	90-123					PHEMA 8V6	27-82
PVG02 VARV	90-123					PHEMA 8V6LN	27-82
PVG03 H8VEB	140-176					PVENV BEV	100-229
PVG03 H8VEK	140-176					PVENV DHV11	310-366
PVG06 VACCC	40-76	131-161	226-269	355-369		PVENV MCV1	252-286
PVG06 VARV	40-76	124-161	255-289	355-369		PVENV MCV2	252-286
PVG07 H8V11	71-88					PVENV THOGV	310-364

PVG08 VACCC	308-338						PVENV VACCC	267-285				
PVG09 VACCV	271-301						PVENV VACCV	267-285				
PVG09 VARV	308-338						PVENV VACCV	267-285				
PVG12 SPVIR	11-45						PVENV VACCV	267-285				
PVG17 HSVI	177-204						PVENV VACCV	267-285				
PVG18 HSVI	174-208						PVENV VACCV	267-285				
PVG1 SPVIR	260-287						PVENV VACCV	267-285				
PVG1 SPV4	267-314						PVENV VACCV	267-285				
PVG22 HSVI	373-400						PVENV VACCV	267-285				
PVG24 HSVI	31-58						PVENV VACCV	267-285				
PVG28 HSVI	263-280						PVENV VACCV	267-285				
PVG2R AMEPV	33-64						PVENV VACCV	267-285				
PVG2 SPVIR	285-328						PVENV VACCV	267-285				
PVG2 SPV4	148-173						PVENV VACCV	267-285				
PVG34 HSVI	38-122						PVENV VACCV	267-285				
PVG37 HSVI	442-488						PVENV VACCV	267-285				
PVG39 HSVI	851-878						PVENV VACCV	267-285				
PVG3L AMEPV	2-28						PVENV VACCV	267-285				
PVG3 SPVIR	18-49						PVENV VACCV	267-285				
PVG3 SPV4	18-52						PVENV VACCV	267-285				
PVG45 HSV9A	138-165						PVENV VACCV	267-285				
PVG46 HSVI	142-168						PVENV VACCV	267-285				
PVG48 HSV9A	360-394						PVENV VACCV	267-285				
PVG4R AMEPV	4-31						PVENV VACCV	267-285				
PVG4 SPVIR	116-146						PVENV VACCV	267-285				
PVG51 HSVI	34-81						PVENV VACCV	267-285				
PVG52 HSV9A	47-74						PVENV VACCV	267-285				
PVG56 HSVI	592-608						PVENV VACCV	267-285				
PVG5 SPVIR	65-92						PVENV VACCV	267-285				
PVG5 SPV4	80-83						PVENV VACCV	267-285				
PVG63 HSVI	550-584						PVENV VACCV	267-285				
PVG64 HSVI	477-504						PVENV VACCV	267-285				
PVG65 HSVI	1213-1284						PVENV VACCV	267-285				
PVG66 HSVI	362-406						PVENV VACCV	267-285				
PVG67 HSVI	1942-1989						PVENV VACCV	267-285				
PVG68 HSVI	281-288						PVENV VACCV	267-285				
PVG72 HSVI	447-481						PVENV VACCV	267-285				
PVG76 HSVI	388-422						PVENV VACCV	267-285				
PVG76 HSVI	200-227						PVENV VACCV	267-285				
PVG7 SPV4	14-44						PVENV VACCV	267-285				
PVG71 BV8	1230-1260						PVENV VACCV	267-285				
PVG13 CV8F	388-426						PVENV VACCV	267-285				
PVG13 CV8L9	399-426						PVENV VACCV	267-285				
PVG13 CV8LY	398-426						PVENV VACCV	267-285				
PVG13 CV8M	398-426						PVENV VACCV	267-285				
PVG13 CV8Q	398-426						PVENV VACCV	267-285				
PVG13 CV8V	398-426						PVENV VACCV	267-285				

PVGL2 CVH22	770-787	809-876	1056-1112		PVG1 SPV4	267-321			
PVGL2 CVM4	843-884	1030-1082			PVG2 HSVI1	117-156	437-629	889-1055	
PVGL2 CYMA5	38-63	581-632	978-1040		PVG24 HSVI1	7-72	74-108		
PVGL2 CYNJH	502-543	888-951			PVG27 HSVI1	164-219			
PVGL2 CYPFS	89-110	882-733	1072-1145	1353-1389	PVG28 HSVI1	263-280			
PVGL2 CVPPU	69-107	880-731	1067-1143	1351-1387	PVG2R AMEPV	26-63	184-218		
PVGL2 CYPFB	488-509	845-921	1128-1165		PVG2 SPV1R	222-256	265-326		
PVGL2 CVPBM	488-509	845-921	1128-1165		PVG2 SPV4	255-310			
PVGL2 EBV	68-102				PVG33 HSVI1	149-183			
PVGL2 FIPV	188-233	454-481	709-738	1072-1148	PVG34 HSVI1	345-378			
PVGL2 IBV6	808-838	876-903	1057-1081		PVG36 HSVI1	17-80			
PVGL2 IBVB	808-835	876-902	1056-1080		PVG37 HSVI1	435-472			
PVGL2 IBVD2	808-838	876-903	1057-1081		PVG38 HSVI1	84-118			
PVGL2 IBVK	808-838	876-902	1056-1080		PVG38 HSVI1	124-158	268-300		
PVGL2 IBVM	808-838	876-902	1056-1080		PVG3 SPV1R	8-49	162-188	203-244	
PVGLB EBV	95-122	631-658			PVG3 SPV4	6-54	67-121		
PVGLB HCMVA	28-86	397-424	440-467	951-978	PVG43 HSVI1	116-150	262-296	324-361	643-677
PVGLB HCMVT	50-88	387-424	435-462	852-879	PVG45 HSVBA	121-162			
PVGLB HSVB1	427-454				PVG46 HSVI1	45-88	938-1078	1251-1321	
PVGLB HSVB2	447-474				PVG48 HSVI1	188-207			
PVGLB HSVBC	428-453				PVG48 HSVBA	360-417	611-866	733-787	
PVGLB HSVE1	443-470	834-861			PVG49 HSVBA	68-102			
PVGLB HSVE4	443-470	816-843			PVG49 HSVBA	4-38			
PVGLB HSVEA	443-470	834-861			PVG4R AMEPV	88-130			
PVGLB HSVEL	443-470	834-860			PVG4 SPV4	34-73	68-123		
PVGLB HSVMD	93-120	352-378			PVG51 HSVI1	28-70	123-157	162-196	
PVGLB MCMVB	381-408	441-475			PVG51 HSVI1	67-127			
PVGLC HSVI1	488-510				PVG51 HSVBA	28-70			
PVGLC HSVIK	488-510				PVG53 HSVI1	355-396			
PVGLC HSVEB	124-151				PVG53 HSVI1	101-135			
PVGLC HSVMB	63-87				PVG54 HSVI1	126-178			
PVGLC HSVMG	62-86				PVG55 HSVBA	151-182	578-612	760-784	1111-1145
PVGLC HSVMM	63-87				PVG55 HSVI1	10-72	88-123		
PVGLC VZVD	295-322				PVG59 HSVBA	168-209			
PVGLC VZVB	295-322				PVG5 SPV1R	65-103			
PVGLC HSV2	111-148				PVG61 HSVI1	286-289			
PVGLF BRBSVA	38-66	154-202	216-243	442-468	PVG63 HSVI1	540-584			
PVGLF BRBSVC	38-66	154-202	216-243	444-471	PVG65 HSVI1	808-839	1213-1264		
PVGLF BRBSVR	38-66	154-202	216-243	444-471	PVG68 HSVI1	154-188	328-410		
PVGLF CDVO	252-263	340-367			PVG67 HSVI1	378-413	501-546	1321-1368	1478-1541
PVGLF HR8V1	38-66	154-202	442-471	488-515	PVG68 HSVI1	245-288			
PVGLF HR8VA	38-66	154-202	213-243	488-518	PVG72 HSVI1	447-484	723-767	912-949	
PVGLF HR8VL	38-66	154-202	213-243	444-471	PVG75 HSVI1	271-305	388-422		
PVGLF HR8VR	38-66	154-202	213-243	444-471	PVG8 SPV1R	5-51			
PVGLF MEABE	228-262				PVG81 HBVB	142-178	1233-1267	2118-2156	3476-3513
PVGLF MEABF	231-268				PVG83 HCMVA	10-44			
					PVG82 CVBF	642-678	850-885	993-1088	1263-1305
					PVG12 CVBL0	550-585	893-1109	1263-1305	

PVGLF MEAGY	228-262						PVGL2 CVBLY	642-676	850-885	893-1108	1283-1305		
PVGLF MUNPM	20-84	447-486					PVGL2 CVBIM	642-676	850-885	893-1108	1283-1305		
PVGLF MUNPR	20-84	447-486					PVGL2 CVBQ	642-676	850-885	893-1108	1283-1305		
PVGLF MUNP8	181-178	428-511					PVGL2 CVBV	642-676	850-885	893-1108	1283-1305		
PVGLF NDVA	181-178	428-512					PVGL2 CVH22	770-816	1055-1112				
PVGLF NDVB	181-178	428-512					PVGL2 CVM4	843-884	1001-1117	1270-1315			
PVGLF NDVI	181-178	428-512					PVGL2 CVM4B	581-632	849-1079	1218-1263			
PVGLF NDVM	181-178	428-512					PVGL2 CVM4H	502-543	882-976	1128-1174			
PVGLF NDVT	181-178	428-512					PVGL2 CVPF8	98-110	448-482	892-733	889-823	1040-1186	1352-1388
PVGLF NDVTG	181-178	428-512					PVGL2 CVPPU	98-110	448-480	890-731	887-821	1038-1184	1351-1387
PVGLF NDVV	181-178	428-512					PVGL2 CVPR8	224-258	488-509	895-889	818-862	1128-1185	
PVGLF PHODV	38-63	221-262				308-338	PVGL2 CVPRM	224-258	488-509	895-889	818-862	1128-1185	
PVGLF PHHC	147-174	210-268					PVGL2 EBV	88-102					
PVGLF PIZH	80-117	141-175				483-528	PVGL2 FIPV	188-245	451-485	895-738	892-826	1043-1189	1355-1392
PVGLF PIZHG	80-117	141-175				483-528	PVGL2 IBV8	701-805	1057-1091				
PVGLF PIZHT	80-117	141-175				483-528	PVGL2 IBV8	437-478	772-804	1056-1080			
PVGLF PIZ8	115-182	207-241				457-487	PVGL2 IBVD2	773-805	1057-1091				
PVGLF PIZ44	115-182	207-241					PVGL2 IBVK	437-478	772-804	1056-1080			
PVGLF RINDK	224-265	458-506					PVGL2 IBVM	437-478	772-804	1056-1080			
PVGLF RINDL	224-265	458-506					PVGLB HCMVA	43-88	128-162	438-484	844-878		
PVGLF REND8	122-149	211-248				480-507	PVGLB HCMVT	22-88	128-162	437-485	845-879		
PVGLF RENDF	122-149	211-245				480-507	PVGLB H8V11	828-880					
PVGLF RENDH	122-149	211-245				480-507	PVGLB H8V1F	827-889					
PVGLF RENDJ	122-149	211-245				480-507	PVGLB H8V1K	827-889					
PVGLF RENDZ	122-149	211-245				480-507	PVGLB H8V1P	828-890					
PVGLF BV41	144-185	241-289				458-486	PVGLB H8V23	828-890					
PVGLF BV8	137-171	417-444					PVGLB H8V2H	828-890					
PVGLF TRTV	124-161	193-200				457-484	PVGLB H8V28	817-871					
PVGLB BEFV	823-857						PVGLB H8V8U	37-71	185-223				
PVGLB BR8VC	92-123						PVGLB H8V81	888-913					
PVGLB H8BV1	63-83						PVGLB H8V82	440-474	848-902				
PVGLB H8BV4	68-107						PVGLB H8V8C	883-900					
PVGLB H8BV6	243-273						PVGLB H8VE1	642-676	811-861				
PVGLB H8VB8	68-83						PVGLB H8VE4	474-518	847-900				
PVGLB H8VE4	271-288						PVGLB H8VEA	642-676	811-861				
PVGLB H8VEB	383-410						PVGLB H8VEB	642-676	811-861				
PVGLB RABVT	488-519						PVGLB H8VEL	642-676	810-860				
PVGLB V8VIG	472-499						PVGLB H8VMD	380-435	648-683	787-845			
PVGLH EBV	548-578	618-648					PVGLB H8V8A	240-288	409-447				
PVGLH HCMVA	107-136	270-297					PVGLB HCMVB	208-260	427-475	893-778	860-884		
PVGLH HCMVT	106-136						PVGLB PRVIF	847-881					
PVGLH H8V8G	82-89	360-403					PVGLB VZVD	92-133	588-630	808-867			
PVGLH H8V8A	388-415						PVGLC H8V11	488-510					
PVGLH HCMVA	47-111						PVGLC H8V1K	488-510					
PVGLM BUNGE	612-646	814-841				1128-1265	PVGLC H8V2	442-476					
PVGLM BUNL7	813-850						PVGLC H8V23	443-477					
PVGLM BUNYW	340-374	804-836				682-709	PVGLC H8V8C	208-269					

PVGLM DUGBV	845-872					PVGLC HSEVB	182-218				
PVGLM HANTB	73-100	883-720				PVGLC HSNMB	53-97				
PVGLM HANTH	75-102					PVGLC HSNMG	82-86				
PVGLM HANTL	75-102					PVGLC HSNMM	53-97				
PVGLM HANTV	75-102					PVGLC PRVIF	183-236				
PVGLM PHV	88-88					PVGLC VZVD	280-321				
PVGLM PUIMH	72-110					PVGLC VZVB	280-321				
PVGLM PUUMB	72-110					PVGLD HSEVA	88-123				
PVGLM SEOUR	73-100	513-640	694-721			PVGLD HSEVB	138-173				
PVGLM SEOUT	73-100	513-640	694-721			PVGLD HSEVK	138-173				
PVGLN BEFV	523-604					PVGLD HSV11	111-146				
PVGLP BEV	48-82	1145-1170	1184-1211	1506-1532		PVGLD HSV2	111-158				
PVGLX HSEVB	17-44	413-444				PVGLF BRBVA	148-202	504-548			
PVGLX PRVRI	427-481					PVGLF BRBVC	148-202	287-302	506-547		
PVGLY JUNIN	14-41					PVGLF BRBVR	148-202	287-302	506-554		
PVGLY LABGG	88-113					PVGLF CDVO	228-297	340-381	588-602		
PVGLY MOPEI	88-113	316-346				PVGLF HRBVI	116-203	287-302	506-548		
PVGLY PIARI	334-375					PVGLF HRBVA	116-202	287-302	506-549		
PVGLY TACV	108-138	316-350				PVGLF HRBVL	116-202	287-302	506-547		
PVGLY TACV6	303-338					PVGLF HRBVR	116-202	287-302	506-549		
PVGLY TACV7	302-337					PVGLF MEASE	116-184	228-269	482-500		
PVGLY TACVT	303-338					PVGLF MEAB1	116-187	231-272	485-503		
PVGLZ HSEVK	17-44					PVGLF MEASY	116-184	228-269	482-500		
PVGLM BPMV	403-430					PVGLF MUMPM	20-84	103-178	235-272	447-502	
PVGLM CP8NV	182-221					PVGLF MUMPR	20-84	103-178	235-272	447-502	
PVGLP BEV	106-148					PVGLF MUMPS	20-84	103-178	235-272	447-502	
PVM1 REOVL	280-317					PVGLF NDVA	117-182	231-272	428-512		
PVM21 REOVD	825-882					PVGLF NDVB	122-182	231-272	428-517		
PVM22 REOVD	824-881					PVGLF NDVI	133-182	238-272	428-517		
PVM2 REOVJ	824-881					PVGLF NDVM	117-182	231-272	428-512		
PVM3 REOVD	188-186	343-370	458-483	631-680		PVGLF NDVT	117-182	231-272	428-517		
PVM2 BRBVA	124-162					PVGLF NDVT8	122-182	231-272	428-517		
PVM2 HRBVA	124-161					PVGLF NDVU	122-182	231-272	428-512		
PVMAT BRBVA	216-246					PVGLF PHODV	28-83	187-268	308-350	533-581	
PVMAT HRBVA	216-246					PVGLF P11HC	123-174	207-267	489-503		
PVMAT INCU	161-186					PVGLF P12H	83-183	477-528			
PVMAT NDVA	247-274					PVGLF P12HQ	83-183	477-528			
PVMAT P12HT	88-123					PVGLF P12HT	83-186	477-528			
PVMAT P13B	201-231					PVGLF P13B	117-182	207-241	480-518		
PVMAT P13H4	201-231					PVGLF P13H4	117-182	207-241	482-532		
PVMAT 5Y41	323-353					PVGLF RINDK	112-180	224-266	448-483		
PVM1 CV8M	176-209					PVGLF RINDL	112-180	224-266	448-508		
PVM1 CYTKE	176-209					PVGLF SEND6	127-188	211-271	483-533		
PVM1 IBV6	21-48	184-218				PVGLF SENDF	127-188	211-271	483-533		
PVM1 IBVB	21-48	184-218				PVGLF SENDH	127-188	218-271	483-533		
PVM1 IBVB2	21-48	184-218				PVGLF SENDJ	127-188	211-271	483-533		
PVM1 IBVK		184-218				PVGLF SENDZ	127-188	211-271	483-533		

PVMP CAMVC		220-264	273-324			PVGLF 5V41	88-188	484-508			
PVMP CAMVO	28-68	220-264	273-324			PVGLF 5V5	103-171	241-276	451-487		
PVMP CAMVE		227-284	273-324			PVGLF TRTV	105-181	180-224	457-488		
PVMP CAMVN		220-264	273-324			PVGLG BEFV	808-812				
PVMP CAMVS		220-264	273-324			PVGLG BR5VC	30-70	104-138			
PVMP CAMVW		220-264	273-324			PVGLG HRSV1	30-81				
PVMP CERV	28-53	100-127				PVGLG HRSV2	30-86				
PVMP SOCMV	4-31	78-118				PVGLG HRSV3	30-85				
PVMSA HPBHE	284-328					PVGLG HRSV4	30-107				
PVMT1 DHV11	38-65	237-284				PVGLG HRSV5	30-85				
PVMT8 MYXVL	163-180					PVGLG HRSV6	30-86				
PVMT9 MYXVL	485-492					PVGLG HRSV7	30-85				
						PVGLG HRSV8	30-81				
						PVGLG HRSVA	30-87				
						PVGLG HRSVL	25-86				
						PVGLG HSE4	271-306				
						PVGLG SIGMA	344-381	464-488			
						PVGLG BYNV	488-523				
						PVGLG VHSVO	383-397				
						PVGLG VSVIG	476-510				
						PVGLH ERV	53-87	160-201	338-380	653-684	
						PVGLH HCMVA	103-137	270-311	693-741		
						PVGLH HCMVT	103-138	682-740			
						PVGLH HSB11	447-481				
						PVGLH H3V1E	447-481				
						PVGLH HSBVG	367-408				
						PVGLH HSBVC	384-418				
						PVGLH HSBV4	334-378	414-455			
						PVGLH HSBV8	327-372	407-448			
						PVGLH HSBVA	32-86	374-453	684-712		
						PVGLH MCHV8	440-474				
						PVGLH PRVKA	226-260				
						PVGLH PRVN3	226-260				
						PVGLH PRVRI	226-260				
						PVGLH VZVD	455-508				
						PVGLH HCMVA	47-111	323-359			
						PVGLM BUNGE	612-667	686-737	1228-1262		
						PVGLM BUNL7	643-677	918-950			
						PVGLM BUNSH	643-677				
						PVGLM BUNYW	340-374	504-563	805-938		
						PVGLM DUGBV	937-989	1238-1300			
						PVGLM HANTB	682-727				
						PVGLM HANTH	72-108				
						PVGLM HANTL	72-108				
						PVGLM HANTV	72-109				
						PVGLM PHV	73-111				
						PVGLM PTPV	149-251				

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	PVME1 CVPF8	98-146	212-267						
	PVME1 CVPFU	212-267							
	PVME1 CVPRM	212-267							
	PVME1 CVTKC	28-62	175-208						
	PVME1 FIPV	212-267							
	PVME1 IBV6	21-55	177-218						
	PVME1 IBVB	21-58	177-218						
	PVME1 IBVB2	21-55	177-218						
	PVME1 IBVK	36-84							
	PVMP CAMVC	187-264	270-324						
	PVMP CAMVD	187-264	270-324						
	PVMP CANVE	187-264	270-324						
	PVMP CAMVN	187-264	270-324						
	PVMP CAMVB	187-264	270-324						
	PVMP CAMVV	187-264	270-324						
	PVMP CERV	212-246							
	PVMP FMVD	217-261							
	PVMP BOCMV	76-118							
	PVMSA HPBDB	272-313	324-361						
	PVMSA HPBDC	271-312	323-360						
	PVMSA HPBDU	234-275	289-323						
	PVMSA HPBDW	272-313	324-361						
	PVMSA HPBGH	210-244							
	PVMSA HPBHE	284-328							
	PVMSA WHV1	208-242							
	PVMSA WHV59	213-247							
	PVMSA WHV7	213-247							
	PVMSA WHV81	213-247							
	PVMT1 DHV11	201-235							
	PVMT1 IAAIN	92-126	174-222						
	PVMT1 IABAN	92-126	174-222						
	PVMT1 IACAO	31-79							
	PVMT1 IAFOW	92-126	174-222						
	PVMT1 IAFRR	92-126	174-222						
	PVMT1 IAFPW	92-126	174-222						
	PVMT1 IALE1	92-126	174-222						
	PVMT1 IALE2	92-126	174-222						
	PVMT1 IAMAN	92-126	174-222						
	PVMT1 IAPOC	92-126	174-222						
	PVMT1 IAPUE	92-126	174-222						
	PVMT1 IAUDD	92-126	174-222						
	PVMT1 IAWIL	92-126	174-222						
	PVMT1 IAZ11	92-126	174-222						
	PVMT1 INBAC	175-208							
	PVMT1 INBAD	175-208							
	PVMT1 INBLE	175-208							
	PVMT1 INBSI	175-208							

PVMT2 INBAC	132-184
PVMT2 INBAD	132-184
PVMT2 INBLE	132-184
PVMT2 INBBI	132-184
PVMT6 MYXVL	40-90 145-187

TABLE VI

Search Results Summary for PCTLZIP,
P1CTLZIP, and P2CTLZIP Motifs

[illegible]

PHEMA MUMPM	133-148		PHEMA IABN	221-237		PHEMA CVHOC	391-408
PHEMA MUMPR	133-148		PHEMA IABUD	234-260		PHEMA IAAIC	322-339
PHEMA MUMPB	133-148		PHEMA IACKA	234-260		PHEMA IABAN	306-323
PHEMA PI1HW	345-380		PHEMA IACKG	231-247		PHEMA IABUD	320-337
PHEMA PI2H	65-80		PHEMA IACKV	230-246		PHEMA IACKA	320-337
PHEMA PI2HT	65-80		PHEMA IADA1	234-260		PHEMA IACKG	316-333
PHEMA RINDK	368-383		PHEMA IADA3	237-253		PHEMA IACKP	302-319
PHEMA SV5	7-84		PHEMA IADCZ	234-260		PHEMA IACKQ	302-318
PHEMA SV5CM	7-84		PHEMA IADH1	221-237		PHEMA IACKS	318-336
PHEMA SV5CP	7-84		PHEMA IADH2	221-237		PHEMA IACKV	315-332
PHEMA SV5LN	7-84		PHEMA IADH3	221-237		PHEMA IADA1	320-337
PVENV DHV11	42-87		PHEMA IADH4	221-237		PHEMA IADA3	322-339
PVFP7 CAPVK	89-104		PHEMA IADH5	221-237		PHEMA IADCZ	320-337
PVRJ8 VACC8	72-87		PHEMA IADH7	221-237		PHEMA IADH1	306-323
PVG01 BPP22	242-257		PHEMA IADH7	221-237		PHEMA IADH2	306-323
PVG01 HSBEB	169-184		PHEMA IADH2	237-253		PHEMA IADH3	306-323
PVG01 HSBV1	210-225	317-332	PHEMA IADH2	234-260		PHEMA IADH4	306-323
PVG06 BPT4	184-198		PHEMA IADH6	221-237		PHEMA IADH6	306-323
PVG07 BPT4	885-900		PHEMA IADH7	237-253		PHEMA IADH7	306-323
PVG08 HSBV1	134-149		PHEMA IAFPR	230-246		PHEMA IADM2	322-338
PVG10 BPH2	183-198		PHEMA IAHAL	236-252		PHEMA IADN2	320-337
PVG10 BPP2A	183-198		PHEMA IAHAR	235-251		PHEMA IADU3	322-339
PVG10 HSBVA	108-124		PHEMA IAHG6	230-246		PHEMA IADN6	306-323
PVG16 BPT1	81-86		PHEMA IAHG7	230-246		PHEMA IADN7	322-339
PVG18 BPT4	468-483		PHEMA IAHG8	230-246		PHEMA IAFPR	315-332
PVG25 BPT4	97-112		PHEMA IAHDE	230-246		PHEMA IAGRE	320-337
PVG29 HSBV1	20-36		PHEMA IAHFO	236-252		PHEMA IAGU2	320-337
PVG30 BPPH8	11-84		PHEMA IAHK6	236-252		PHEMA IAGUA	318-336
PVG38 BPOX2	22-37		PHEMA IAHK7	236-252		PHEMA IAHAL	321-338
PVG39 HSBVA	108-123		PHEMA IAHLE	230-246		PHEMA IAHG6	315-332
PVG37 BPT2	1253-1268		PHEMA IAHLO	230-246		PHEMA IAHG7	315-332
PVG37 HSBV1	284-289		PHEMA IAHMI	236-252		PHEMA IAHCD	318-332
PVG55 HSBV1	22-37	143-168	PHEMA IAHNM	236-252		PHEMA IAHDE	315-332
PVG58 HSBV1	288-293		PHEMA IAHRO	236-252		PHEMA IAHFO	321-338
PVG59 HSBV1	102-117		PHEMA IAHBA	236-252		PHEMA IAHK6	321-338
PVG59 HSBV1	207-282		PHEMA IAHBP	230-246		PHEMA IAHK7	321-338
PVG65 HSBV1	818-533		PHEMA IAHBW	230-246		PHEMA IAHLE	318-332
PVG8 BPPH2	234-249		PHEMA IAHTE	236-252		PHEMA IAHLO	316-332
PVG8 BPP2A	234-249		PHEMA IAHTO	236-252		PHEMA IAHMI	321-338
PVG8 BPP1R	67-72		PHEMA IAHUR	236-252		PHEMA IAHNM	321-338
PVG8 BPPHX	234-249		PHEMA IAKIE	236-251		PHEMA IAHNN	315-332
PVG12 CVBF	284-279		PHEMA IALEN	235-251		PHEMA IAHPR	321-338
PVG12 CVBL9	284-279		PHEMA IAMAA	233-249		PHEMA IAHRO	321-338
PVG12 CVBLY	284-279		PHEMA IAMAB	238-254		PHEMA IAHSA	315-332
PVG12 CVBM	284-279		PHEMA IAMAO	237-253		PHEMA IAHSP	315-332
PVG13 CVBQ	284-279		PHEMA IAME1	237-253		PHEMA IAH8W	315-332
PVG13 CVBV	284-279		PHEMA IAME2	237-253		PHEMA IAHTE	321-338

PVGL2 CVPP6	442-457	PHEMA IAME6	221-237			PHEMA IAHTO	321-338
PVGL2 CVPPU	440-455	PHEMA IAMIN	85-101	231-247		PHEMA IAHUR	321-338
PVGL2 CVPR6	218-233	PHEMA IANT6	237-263			PHEMA IAJAP	317-334
PVGL2 CVPRIM	218-233	PHEMA IAU07	231-237			PHEMA IAMAA	318-338
PVGL2 IBV6	1056-1071	PHEMA IAS22	234-260			PHEMA IAMAB	324-341
PVGL2 IBV8	1056-1071	PHEMA IAS22	234-260			PHEMA IAMAO	322-339
PVGL2 IBVD2	1056-1071	PHEMA IAS22	234-260			PHEMA IAME1	322-339
PVGL2 IBVK	1056-1070	PHEMA IASTA	230-246			PHEMA IAME2	322-339
PVGL2 IBVM	1056-1070	PHEMA IATAI	236-261			PHEMA IAME6	306-323
PVGLB HSB8A	701-716	PHEMA IATKM	234-260			PHEMA IAMIN	316-333
PVGLB PRVIF	203-218	PHEMA IATKO	233-248			PHEMA IANT6	322-339
PVGLC HSBVC	478-480	PHEMA IATKR	230-248			PHEMA IAPIL	320-337
PVGLC HSBVE4	444-459	PHEMA IATKW	228-248			PHEMA IAU07	306-323
PVGLC HSBVE	427-442	PHEMA IAU00	237-263			PHEMA IARUD	320-337
PVGLC PRVIF	448-461	PHEMA IAU58	238-261			PHEMA IAS62	320-337
PVGLD H8V11	78-84	PHEMA IAV17	238-264			PHEMA IAS62	321-338
PVGLD H8V2	78-84	PHEMA IAXIA	238-261			PHEMA IASTA	316-332
PVGLF H8BVA	285-280	PHEMA IAZCO	237-263			PHEMA IATKM	320-337
PVGLF H8BVC	285-280	PHEMA IAZH2	221-237			PHEMA IAU00	322-339
PVGLF H8BVR	285-280	PHEMA IAZH3	221-237			PHEMA IAV17	323-340
PVGLF H8BV1	285-280	PHEMA IAZUK	237-263			PHEMA IAZCO	322-339
PVGLF H8BVA	285-280	PHEMA INBAA	116-131	286-310		PHEMA IAZH2	306-323
PVGLF H8BVL	285-280	PHEMA INBBE	123-139	303-318		PHEMA IAZH3	306-323
PVGLF H8BVR	285-280	PHEMA INBBO	116-132	283-308		PHEMA IAZUK	322-339
PVGLF H8BVS	285-280	PHEMA INBEN	123-139	301-316		PHEMA MUMPM	101-118
PVGLF MUMPS	8-94	PHEMA INBFU	108-124	286-301		PHEMA MUMPS	101-118
PVGLI VZVD	278-283	PHEMA INBGL	119-135	286-311		PHEMA NDVA	93-110
PVGLM HANTB	800-816	PHEMA INBHL	116-132	283-308		PHEMA NDVB	93-110
PVGLM PTPV	743-758	PHEMA INBHK	108-124	288-303		PHEMA NDVO	93-110
PVGLM SEOUR	801-816	PHEMA INBIB	120-136	289-314		PHEMA NDVH	93-110
PVGLM SEOUS	800-815	PHEMA INBID	123-139	302-317		PHEMA NDVI	93-110
PVGLY L898G	420-441	PHEMA INBLE	113-129	282-307		PHEMA NDVM	93-110
PVGLY L898J	427-442	PHEMA INBMD	116-132	286-311		PHEMA NDVQ	93-110
PVGLY MOPEI	426-440	PHEMA INBME	108-124	288-303		PHEMA NDVTG	93-110
PVM3 REOVD	521-536	PHEMA INBNA	123-139	301-316		PHEMA NDVV	93-110
PVMB8 HPBG8	360-366	PHEMA INBOR	119-135	288-313		PHEMA PHODV	38-63
PVMB8 HPBV8	187-202	PHEMA INBBI	116-132	284-308		PHEMA PI1HW	488-503
PVMB8 WHV1	378-393	PHEMA INBSJ	123-139	303-318		PHEMA PI3B	111-128
PVMB8 WHV69	383-398	PHEMA INBUS	108-124	286-301		PHEMA PI3H4	111-128
PVMB8 WHV7	383-398	PHEMA INBVI	133-148			PHEMA PI3HT	111-128
PVMB8 WHV8	383-398	PHEMA INBVK	133-148			PHEMA PI3HU	111-128
PVMB8 WHV8I	383-398	PHEMA INBYB	133-148			PHEMA PI3HV	111-128
PVMB8 WHVW6	234-248	PHEMA MUMPM	133-148			PHEMA PI3HW	111-128
PVMT2 IANIN	25-40	PHEMA MUMPS	133-148			PHEMA PI3HX	60-97
PVMT2 JASAN	25-40	PHEMA PI1HW	346-360			PHEMA PI4H4	
PVMT2 JFOVW	25-40	PHEMA PI2H	68-81				
PVMT2 JAPR	25-40	PHEMA PI2HT	68-81				
PVMT2 JAPW	25-40						

PVMT2 IALE1	26-40	PHEMA P13B	324-340				PHEMA 8V41	86-102
PVMT2 IALE2	25-40	PHEMA P13H4	324-340				PHEMA 8V5	84-101
PVMT2 IAMAN	26-40	PHEMA P13HA	324-340				PHEMA 8V6CM	84-101
PVMT2 IAPUE	26-40	PHEMA P13HT	324-340				PHEMA 8V6CP	84-101
PVMT2 IASIN	26-40	PHEMA P13HU	324-340				PHEMA 8V6LN	84-101
PVMT2 IAUDO	26-40	PHEMA P13HV	324-340				PVF05 VACCC	280-287
PVMT2 IAWIL	26-40	PHEMA P13HW	324-340				PVF06 VACCP	280-287
PVMT8 MYXVL	226-241	PHEMA P13HX	324-340				PVF08 VACCV	281-288
		PHEMA RINDK	368-383				PVF09 VACCC	176-183
		PHEMA 8V6	7-84				PVF08 VACCV	176-183
		PHEMA 8V6CM	7-84				PVG27 H8V8A	208-228
		PHEMA 8V6CP	7-84				PVG28 H8V11	173-180
		PHEMA 8V6LN	7-94				PVG38 H8V11	848-865
		PVENV D8V11	42-57				PVG43 H8V11	108-126
		PVENV EAV	26-41				PVG07 H8V11	171-188
		PVF22 FQWTV	88-104				PVG72 H8V11	1262-1289
		PVPF7 CAPVK	89-104				PVGf1 IBVB	3073-3080
		PVRUS VACC8	72-87				PVGL2 IBV6	1084-1111
		PVG01 H8VEB	168-184				PVGL8 H8VE1	736-753
		PVG08 H8V11	208-225			317-332	PVGL8 H8VE4	876-892
		PVG10 H8V8A	134-149				PVGL8 H8VEA	736-753
		PVG11 H8V11	108-124				PVGL8 H8VEB	736-753
		PVG12 H8V11	103-119				PVGL8 H8VEL	736-753
		PVG1 8PV1R	270-286				PVGL8 LTV8	597-614
		PVG38 H8V11	76-82				PVGL8 LTV8	607-624
		PVG38 BPOX2	20-35				PVGLC PRVIF	180-197
		PVG36 H8V8A	22-37				PVGL6 VZVD	489-488
		PVG37 H8V11	108-123				PVGLF 8V6	401-418
		PVG41 H8V11	284-289				PVGLH HCMVA	385-382
		PVG46 H8V11	244-260				PVGLH HCMVT	394-381
		PVG55 H8V11	1244-1260				PVGLH H8V11	245-282
		PVG60 H8V11	22-37			143-158	PVGLH H8V1E	245-262
		PVG68 H8V11	288-283				PVGLI H8V11	43-60
		PVG68 H8V11	101-117				PVGLM BUNL7	81-88
		PVG68 H8V8A	130-146			330-346	PVGLM BUN8H	81-88
		PVG68 H8V11	287-282				PVGLM PUUMH	712-729
		PVG68 H8V11	382-378			518-533	PVGLM PUUMS	712-729
		PVG71 H8V8A	89-105				PVGLM RVFV	344-361
		PVG8 BPPH2	234-249				PVGLM RVFVZ	344-381
		PVG8 BPPZA	234-249				PVGLY LA68G	12-94
		PVG8 8PV1R	57-72				PVGLY LA68J	12-84
		PVGf1 IBVB	2210-2228				PVGLY LYCVA	12-94
		PVGL2 CVBF	123-139			174-190	PVGLY LYCWN	12-84
		PVGL2 CVBL9	123-139			174-190	PVGLY MOPEI	12-94
		PVGL2 CVBLV	123-139			174-190	PVM1 REOVD	280-287
		PVGL2 CVBM	123-139			174-190	PVM1 REOVL	280-287
		PVGL2 CVBQ	31-47			174-190		
						284-278		
						284-278		
						284-279		
						284-279		
						174-190		
						123-139		
						31-47		
						284-278		
						174-190		
						123-139		
						284-279		
						174-190		

	PVGL2 CVBV	123-139	174-180	284-279	PVMAT CDVO	148-166
	PVGL2 CVM4	95-111	1287-1283		PVMAT MEAS1	87-104
	PVGL2 CVM46	95-111	1216-1231		PVMP CAMVC	147-184
	PVGL2 CVMJH	95-111	1126-1142		PVMP CAMVD	147-184
	PVGL2 CVPF8	442-457	600-816	1274-1290	PVMP CAIWE	147-184
	PVGL2 CVPFU	440-455	504-518	788-814	PVMP CAMVN	147-184
	PVGL2 CVPR8	218-233	578-592	1050-1088	PVMP CAMVS	147-184
	PVGL2 CVPRM	218-233	578-592	1050-1088	PVMP CAMVV	147-184
	PVGL2 FIPV	803-819	1277-1283		PVMSA HPEBVO	11-94
	PVGL2 IBV6	1058-1071			PVMSA HPEBV2	185-202
	PVGL2 IBV8	1058-1070			PVMSA HPEBV4	185-202
	PVGL2 IBVD2	1058-1071			PVMSA HPEBA	174-181
	PVGL2 IBVK	1058-1070			PVMSA HPEBVD	11-94
	PVGL2 IBVM	1058-1070			PVMSA HPEBJ	174-181
	PVGLB HSB8A	701-716			PVMSA HPEBN	11-94
	PVGLB PRVF	203-218			PVMSA HPEBO	174-181
	PVGLB VZVD	622-638			PVMSA HPEBP	185-202
	PVGLC HSBVC	476-480			PVMSA HPEBR	185-202
	PVGLC HSVE4	444-458			PVMSA HPEBS	11-94
	PVGLC HSVEB	427-442			PVMSA HPEBVW	174-181
	PVGLC PRVF	448-461			PVMSA HPEBY	174-181
	PVGLC VZVD	150-166			PVMSA HPEBZ	174-181
	PVGLD H8V1	150-166			PVMT2 IAANN	28-42
	PVGLD H8V2	76-84			PVMT2 IABAN	28-42
	PVGLF PRVR1	3-94			PVMT2 IAFOW	28-42
	PVGLF BR8VA	205-221	265-280		PVMT2 IAFPR	26-42
	PVGLF BR8VC	205-221	265-280		PVMT2 IAFPW	26-42
	PVGLF BR8VR	205-221	265-280		PVMT2 IALE1	26-42
	PVGLF COVO	398-414			PVMT2 IALE2	26-42
	PVGLF HR8V1	205-221	265-280		PVMT2 IAMAN	26-42
	PVGLF HR8VA	205-221	265-280		PVMT2 IAPUE	26-42
	PVGLF HR8VL	205-221	265-280		PVMT2 IASIN	26-42
	PVGLF HR8VR	205-221	265-280		PVMT2 IAUDO	26-42
	PVGLF MEABE	286-302			PVMT2 IAWIL	28-42
	PVGLF MEAB1	289-305				
	PVGLF MEASY	286-302				
	PVGLF MUMPM	276-292				
	PVGLF MUMPR	276-292				
	PVGLF MUMPS	6-94	276-292			
	PVGLF NDVA	273-289				
	PVGLF NDVB	273-289				
	PVGLF NDVM	273-289				
	PVGLF NDVT	273-289				
	PVGLF NDVTG	273-289				
	PVGLF NDVU	273-289				
	PVGLF P4QDV	298-285	367-383			

	PVGLF RINDK	282-298							
	PVGLF RINDL	282-298							
	PVGLF TRTV	176-101							
	PVGLI VZVD	278-283							
	PVGLM HANTB	356-371							
	PVGLM HANTR	498-515							
	PVGLM HANTL	498-515							
	PVGLM HANTV	498-515							
	PVGLM PTPV	743-758							
	PVGLM PUUMH	509-528							
	PVGLM PUIMS	509-528							
	PVGLM SEOUR	356-371							
	PVGLM SEOUS	356-371							
	PVGLM UUK	828-842							
	PVGLP BEV	808-895							
	PVGLY LAGSG	12-94							
	PVGLY LABSJ	12-94							
	PVGLY LYCYA	12-94							
	PVGLY LYGVW	12-94							
	PVGLY MOPEI	12-94							
	PVGLY PIARV	12-94							
	PVGNM CMNV	1021-1037							
	PVM3 REOVD	521-538							
	PVMAT MUMPS	191-207							
	PVMAT NDVA	135-151							
	PVMAT NDVB	135-151							
	PVMAT PIZHT	189-205							
	PVMAT SV41	198-205							
	PVMAT SV5	98-114							
	PVMP CAMVC	118-134							
	PVMP CAMVD	118-134							
	PVMP CAMVE	118-134							
	PVMP CAMVN	118-134							
	PVMP CAMVS	118-134							
	PVMP CAMVW	118-134							
	PVMP FMVD	116-131							
	PVMSA HPBGQ	380-395							
	PVMSA HF8V9	187-202							
	PVMSA WHV1	375-383							
	PVMSA WHV59	383-398							
	PVMSA WHV7	383-398							
	PVMSA WHV8	383-398							
	PVMSA WHV81	383-398							
	PVMSA WHVWB	234-249							
	PVMT2 IAANN	28-40							
	PVMT2 IABAN	25-40							
	PVMT2 IAFOW	28-40							

TABLE VII

**Search Results Summary for P3CTLZIP, P4CTLZIP,
P5CTLZIP, and P6CTLZIP Motifs**

[illegible]

PVMT1 VACCV	83-101	128-144	PVGL2 CVMA4	888-1018	PVENV THQV	358-378		PHEMA P12H	13-34	
PVMT1 REOVD	227-245		PVGL2 CVMA5	847-888	PVG01 VACCC	288-318		PHEMA P12HT	13-34	
PVMT1 REOVL	227-245		PVGL2 CVMLH	858-877	PVG01 VACCV	237-257		PHEMA SV6	7-28	378-400
PVMAT HRBVA	44-62		PVGL2 CVPF8	84-83	PVG01 VAR	288-318		PHEMA SV5CM	7-28	378-400
PVMAT NDVA	180-208		PVGL2 CVPPU	84-83	PVG08 VACCC	31-51		PHEMA SV6CP	7-28	378-400
PVMAT NDVB	180-208		PVGL2 CVPRB	814-833	PVG08 VAR	31-51		PHEMA SV6LN	7-28	378-400
PVMP CAMVC	183-201		PVGL2 CVPRM	814-833	PVG08 BPFF1	25-45		PVG01 HSEVB	188-190	
PVMP CAMVD	183-201		PVGL2 FIPV	1041-1080	PVG12 HSNV1	151-171		PVG01 HSNV1	589-610	
PVMP CAMVE	183-201		PVGL2 IBV6	588-607	PVG22 HSNV1	300-320		PVG23 HSNV1	314-335	
PVMP CAMVN	183-201		PVGL2 IBV8	587-608	PVG38 HSNV1	848-868	870-880	PVG37 BPOX2	66-88	
PVMP CAMV8	183-201		PVGL2 IBVD2	588-607	PVG51 HSNV1	28-49		PVG43 HSNV1	167-178	
PVMP CAMVW	183-201		PVGL2 IBVK	587-608	PVG83 HSNV1	338-358		PVG55 HSNV1	288-308	
PVMP CAMVD	180-188		PVGL2 IBVM	587-608	PVG88 HSNV1	117-137		PVG55 HSNV8A	65-108	
			PVGLB HCMVA	705-725	PVG74 HSNV8A	124-144		PVG58 HSNV1	1155-1176	
			PVGLB HCMVT	707-728	PVGL2 IBV8	328-348		PVG58 HSNV8A	268-287	
			PVGLB HSNV8U	117-138	PVGL2 IBV8	327-347		PVG80 HSNV1	30-51	
			PVGLB ILTV8	268-275	PVGL2 IBVD2	328-348		PVG83 HSNV1	238-259	
			PVGLB ILTV8	268-285	PVGL2 IBVD3	328-348		PVG80 HSNV1	1886-1877	
			PVGLB ILTVT	268-285	PVGL2 IBVK	327-347		PVG83 HSNV1	167-178	
			PVGLC HSNV11	3-84	PVGL2 IBVM	327-347	378-388	PVG83 HCMVA	1259-1280	
			PVGLC HSNV1K	3-84	PVGL2 IBVU2	310-330		PVGL2 CVBL9	1258-1280	
			PVGLC HSNVBC	475-484	PVGLB EB	732-752		PVGL2 CVBL9	1258-1280	
			PVGLC CHAV	436-455	PVGLB HCMVA	750-770		PVGL2 CVBM	1258-1280	
			PVGLG RABVH	372-381	PVGLB HCMVT	751-771		PVGL2 CVBQ	1258-1280	
			PVGLI HSEVB	44-83	PVGLB HSNV23	75-98		PVGL2 CVBV	1258-1280	
			PVGLI VZVO	278-287	PVGLB HSNV2H	75-98		PVGL2 CVMA4	1317-1338	
			PVGLM BUNGE	117-138	PVGLB HSNV28	65-95		PVGL2 CVMA5	1285-1288	
			PVGLM PHV	152-171	PVGLB HSNV6U	72-92		PVGL2 CVMLH	1176-1187	
			PVGLM PTPV	987-1016	PVGLB HSNV82	278-289		PVGLB HSNV11	83-104	
			PVGLM PUJNH	155-174	PVGLB HSNV8A	83-93		PVGLB HSNV1F	82-103	
			PVGLM PUJNH	155-174	PVGLB MCMV8	738-758		PVGLB HSNV1K	82-103	
			PVGLM RVFV	830-849	PVGLF P13H4	283-303		PVGLB HSNV1P	83-104	
			PVGLM RVFVZ	830-849	PVGLG RABVE	454-474		PVGLB MCMV9	138-158	
			PVGLM UUK	658-674	PVGLG RABVH	454-474		PVGLC PRVIF	448-457	
			PVGLY LYCVW	89-108	PVGLG RABVP	454-474		PVGLF CDVO	338-357	
			PVGNB CPMV	1185-1194	PVGLG RABV8	454-474		PVGLF MEABE	224-245	
			PVMS REOVD	521-540	PVGLG RABVT	454-474		PVGLF MEAB1	227-248	
			PVME1 CVBM	171-190	PVGLH MCMV8	870-890		PVGLF MEASY	224-245	
			PVME1 CVH22	136-155	PVGLM BUNL7	1325-1345		PVGLF MUMPM	448-467	
			PVME1 CVPF8	174-183	PVGLM BUNBH	986-1016		PVGLF MUMPR	448-467	
			PVME1 CVPPU	174-183	PVGLM BUNYW	888-1018		PVGLF MUMPS	448-467	
			PVME1 CVPRM	174-183	PVGLM HANTH	1000-1020		PVGLF PHODV	305-326	
			PVME1 CVTKE	171-180	PVGLM HANTH	1001-1021		PVGLF PIHC	458-477	
					PVGLM HANTL	1001-1021		PVGLF PIH	450-471	
					PVGLM HANTV	1001-1021		PVGLF PI2HG	450-471	
					PVGLM RVFVZ	1158-1178		PVGLF PI2HT	450-471	
					PVGLM SEOUR	1000-1020		PVGLF PI3B	408-428	453-474

	PVGLM SEQUS	988-1016	PVGLF P3H4	483-474
	PVGLM UIK	926-946	PVGLF RINDK	220-241
	PVGLY LYCVA	12-32	PVGLF RINDL	220-241
	PVGLY LYCVW	12-32	PVGLF SENDS	460-481
	PVGLY PIARV	12-32	PVGLF SENDF	460-481
	PVGNB CPMV	141-161	PVGLF SENDE	460-481
	PVMAT MUMF@	310-330	PVGLF SENDJ	460-481
	PVMAT NDVA	308-328	PVGLF SENDZ	460-481
	PVMAT NDVB	308-328	PVGLF SV41	453-474
	PVMAT PI2HT	308-328	PVGLF SV6	448-467
	PVMAT PI4HA	312-332	PVGLH HCMVA	981-712
	PVMAT PI4HB	312-332	PVGLH HCMVT	980-711
	PVMAT SV41	308-328	PVGLH HSVE4	304-326
	PVMAT SV6	308-328	PVGLH HSVEB	287-318
	PVME1 IBV8	74-84	PVGLH HSBVA	858-879
	PVME1 IBV82	74-84	PVGLI HSV2	2-23
	PVME1 IBVK	74-84	PVGLI HSV23	2-23
	PVMSA HPBD8	201-221	PVGLM BUNGE	187-218
	PVMSA HPBG8	208-228	PVGLM BUNL7	180-211
	PVMSA HPBHE	283-313	PVGLM BUNSH	180-211
	PVMSA WHV1	207-227	PVGLM BUNYW	183-214
	PVMSA WHV60	212-232	PVGLY LABEG	237-268
	PVMSA WHV7	212-232	PVGLY LAGSJ	238-269
	PVMSA WHV8	212-232	PVGPS EBV	87-88
	PVMSA WHV81	212-232	PVM01 VACCC	281-302
	PVMSA WHVW8	63-83	PVM01 VACCV	230-261
			PVMAT HR9VA	188-180
			PVMAT RINDK	200-221
			PVMAT TRTV	122-143
			PVME1 CVHOC	84-86
			PVMSA HPBD8	201-222
			PVMSA HPBV0	70-81
			PVMSA HPBV2	244-265
			PVMSA HPBV4	244-265
			PVMSA HPBV9	244-265
			PVMSA HPBVA	233-264
			PVMSA HPBVD	70-81
			PVMSA HPBV1	233-264
			PVMSA HPBVJ	233-264
			PVMSA HPBVL	233-264
			PVMSA HPBVN	70-81
			PVMSA HPBVO	233-264
			PVMSA HPBPV	244-286
			PVMSA HPBVR	244-286
			PVMSA HPBS8	70-81
			PVMSA HPBVW	233-264
			PVMSA HPBVY	233-264

[illegible]

TABLE VIII

Search Results Summary for P7CTLZIP,
P8CTLZIP, and P9CTLZIP Motifs

[illegible]

PHEMA IAVI7	38-60		PVGL2 IBVK	196-218	PVGLB HSMVD	588-613		
PHEMA IAX31	37-59		PVGL2 IBVM	195-218	PVGLB ILTV8	587-621		
PHEMA IAZCO	37-59		PVGL2 IBVU1	178-201	PVGLB ILTV8	607-631		
PHEMA IAZH2	21-43		PVGL2 IBVU2	178-201	PVGLB ILTVT	607-631		
PHEMA IAZH3	21-43		PVGL2 IBVU3	178-201	PVGLB HSMV11	413-437		
PHEMA IAZUK	37-59		PVGLB HCMVA	535-558	PVGLB VZVD	489-483		
PHEMA PHODV	38-66		PVGLB HCMVT	536-558	PVGLF SV6	401-425		
PHEMA PIZH	68-87		PVGLB HSMVA	493-506	PVGLH HCMVA	574-588		
PHEMA PIZHT	68-87		PVGLB HCMV8	588-589	PVGLH HCMVT	573-587		
PVPF7 CAPVK	89-111		PVGLC HSMV11	487-480	PVGLH HSMV11	443-487	803-827	
PVFUS VACC8	72-84		PVGLC HSMV1K	487-480	PVGLH HSMV1E	443-487	803-827	
PVG01 HSMV1	317-338		PVGLC HSMV2	435-458	PVGLM BUNL7	31-55		
PVG03 VACC	50-72		PVGLC HSMV23	436-459	PVGLM BUNSH	31-55		
PVG03 VARV	50-72		PVGLM BUNL7	1387-1410	PVGLM HANTH	694-718		
PVG04 VACC	11-33		PVGLM BUNSH	1387-1410	PVGLM RVFV	344-368		
PVG04 VARV	11-33		PVGLM UUK	886-889	PVGLM RVPVZ	344-368		
PVG18 HSMV1	68-110		PVGLY JUNIN	12-35	PVGLM UUK	561-585		
PVG28 HSMV1	173-185		PVGLY LAS8Q	12-35	PVGNM CPMV	311-335		
PVG28 HSMV1	20-42		PVGLY LAS8J	12-35	PVGP2 EBV	667-681		
PVG46 HSMV1	134-156		PVGLY LYCVA	12-35	PVGP3 EBV	654-678		
PVG48 HSMVA	71-93		PVGLY LYCVW	12-35	PVM1 REOVD	280-304		
PVG58 HSMVA	266-288		PVGLY MOPEI	12-35	PVM1 REOVL	280-304		
PVG58 HSMV1	267-288		PVGLY TACV	12-35	PVM21 REOVD	168-192		
PVG5 8PV4	42-64		PVGLY TACV6	12-35	PVM22 REOVD	168-192		
PVG60 HSMV1	53-75		PVGLY TACV7	12-35	PVM2 REOVJ	168-192		
PVG65 HSMV1	1347-1369		PVGLY TACVT	12-35	PVM2 REOVL	168-192		
PVG8 8PV1R	60-82		PVGNM CPMV	741-764	PVMAT MEAB1	87-111		
PVGL2 IBV6	1056-1078		PVM1 REOVD	324-347	PVMAT 6SPVB	314-338		
PVGL2 IBVB	1056-1077		PVM1 REOVL	464-477	PVME1 CVBM	137-161		
PVGL2 IBVD2	1056-1078		PVMAT MUMP8	227-250	PVME1 CVHOC	137-161		
PVGL2 IBVK	1056-1077		PVMSA HPBDB	268-292	PVME1 CVTKE	137-161		
PVGL2 IBVM	1056-1077		PVMSA HPBDC	268-291	PVME1 IBV6	74-88		
PVGLB HSMV1	117-138		PVMSA HPBDU	231-254	PVME1 IBVB	74-88		
PVGLB HSMV2	746-767		PVMSA HPBDW	268-292	PVME1 IBVB2	74-88		
PVGLC HSMVB	389-421		PVMSA HPSHE	236-259	PVME1 IBVK	74-88		
PVGLC HSMVMQ	389-420				PVMSA HPSGB	271-285		
PVGLC HSMVM	389-421				PVMSA WHV1	269-283		
PVGLP BR8VA	286-287	482-504			PVMSA WHV59	274-288		
PVGLF BR8VC	484-506				PVMSA WHV7	274-288		
PVGLF BR8VR	484-506				PVMSA WHV8	274-288		
PVGLF HR8V1	484-506				PVMSA WHV81	274-288		
PVGLF HR8VA	484-506				PVMSA WHVW8	126-149		
PVGLF HR8VL	484-506							
PVGLF HR8VR	484-506							
PVGLF TRTV	452-474							
PVGL8 HNV	77-99							
PVGL8 VHSVO	406-428							

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TABLE IX

Search Results Summary for P12CTLZIP Motif

[illegible]

[illegible]

-67-

PHEMA INBME	110-132	286-311							
PHEMA INBNA	109-124	288-303							
PHEMA INBOR	123-139	301-316							
PHEMA INBSI	123-139	301-316							
PHEMA INBSJ	119-138	298-313							
PHEMA INBUS	116-132	294-309							
PHEMA INBVI	116-132	296-311							
PHEMA INBYK	123-139	303-318							
PHEMA INBYB	109-124	286-301							
PHEMA INCCA	442-468								
PHEMA INCEN	430-464								
PHEMA INCOL	430-464								
PHEMA INCXY	429-463								
PHEMA INCJH	443-467								
PHEMA INCKY	428-463								
PHEMA INCM I	429-463								
PHEMA INCNA	428-463								
PHEMA INCP1	430-464								
PHEMA INCP2	430-464								
PHEMA INCP3	430-464								
PHEMA INCTA	430-464								
PHEMA INCYA	430-464								
PHEMA MUMPM	133-148	228-248	397-417						
PHEMA MUMPR	101-126	133-148	397-417						
PHEMA MUMP8	101-128	133-148	397-417						
PHEMA NDVA	93-110								
PHEMA NDVB	93-110								
PHEMA NDVD	93-110								
PHEMA NDVH	93-110								
PHEMA NDVI	93-110								
PHEMA NDVM	93-110								
PHEMA NDVG	93-110								
PHEMA NDVV	93-110								
PHEMA PHODV	38-58	213-234	493-613						
PHEMA PI1HW	28-53	322-342	346-380	488-603					
PHEMA PIZH	13-40	66-86	118-136						
PHEMA PIZHT	13-40	66-86	118-136						
PHEMA PI3B	111-128	272-289	324-340						
PHEMA PI3HA	111-128	272-289	324-340						
PHEMA PI3HT	111-128	272-289	324-340						
PHEMA PI3HU	111-128	272-289	324-340						
PHEMA PI3HV	111-128	272-289	324-340						
PHEMA PI3HW	111-128	272-289	324-340						
PHEMA PI3HX	111-128	272-289	324-340						
PHEMA PI4HA	50-67								

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-73-

PVGLM PTPV	743-765	897-1016	1276-1302						
PVGLM PUUMH	155-174	508-525	712-729						
PVGLM PUUMS	155-174	508-525	712-729	1092-1117					
PVGLM RVFV	53-80	344-368	830-856						
PVGLM RVFVZ	53-80	344-368	830-856	1156-1176					
PVGLM SEOUR	355-371	693-718	901-916	1000-1020					
PVGLM SEOUS	355-371	692-717	900-916	999-1019					
PVGLM UUK	581-585	655-674	826-842	926-952	906-989				
PVGLP BEV	430-452	869-885	1089-1124	1546-1568					
PVGLX PRVRI	149-176								
PVGLY JUNIN	12-38								
PVGLY LASEG	12-38	237-258	426-448						
PVGLY LASEJ	12-38	238-259	427-448						
PVGLY LYCVA	12-38								
PVGLY LYCVW	12-38	89-108							
PVGLY MOPEI	12-38	428-447							
PVGLY PIARV	12-38	441-469							
PVGLY TACV	12-38								
PVGLY TACV6	12-38								
PVGLY TACV7	12-38								
PVGLY TACVT	12-38								
PVGNB CPMV	141-161	568-584	757-783	1110-1135	1185-1194				
PVGNM BPMV	678-686								
PVGNM CPMV	311-335	741-784	1021-1037						
PVGP2 EBV	657-681								
PVGP3 EBV	854-878								
PVGP8 EBV	67-88								
PVM01 VACC	134-159	177-185	281-302						
PVM01 VACCV	83-108	126-144	230-251						
PVM1 REOVD	141-168	227-245	280-304	324-347	414-436	454-477			
PVM1 REOVL	141-168	227-245	280-304	414-436	454-477				
PVM21 REOVD	168-182								
PVM22 REOVD	108-192								
PVM2 REOVJ	168-182								
PVM2 REOVL	168-192								
PVM3 REOVD	304-328	521-540							
PVMAT BR3VA	37-62								
PVMAT CDVO	148-165	293-309							
PVMAT HR3VA	44-62	139-160							
PVMAT LPMV	311-338								
PVMAT MEASE	283-309								
PVMAT MEASH	283-309								
PVMAT MEAS1	67-111								
PVMAT MEASU	283-308								
PVMAT MUMPS	191-207	247-250	310-330						
PVMAT NDVA	136-151	180-208	308-329						
PVMAT NDVB	136-151	180-208	308-329						

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TABLE X

Search Results Summary for P23CTLZIP Motif

-78-

PENV HV1W1	730-763				
PENV HV1W2	721-784				
PENV HV1Z2	264-286	727-760			
PENV HV1Z3	260-281				
PENV HV1Z8	265-288	728-762			
PENV HV1Z8	265-288				
PENV HV2BE	761-811				
PENV HV2D1	772-802				
PENV HV2G1	772-802				
PENV HV2NZ	777-814				
PENV HV29B	743-776				
PENV J8RV	288-332	484-518			
PENV MMTV8	438-472				
PENV MMTV9	438-472				
PENV R8VP	633-670				
PENV 8FV1	44-76	492-530			
PENV 8FV3L	48-82	550-588			
PENV 8IVCZ	746-778				
PENV 8IVGB	247-277	383-388			
PENV 8IVM1	789-800				
PENV 8IVMK	768-789				
PENV 8IVML	611-645	764-798			
PENV 8IV84	468-488				
PENV 8IV8P	482-490	810-840			
PHEMA CDVO	200-234				
PHEMA IABUD	23-55				
PHEMA IACKA	23-55				
PHEMA IACKV	517-547				
PHEMA IADA1	23-55				
PHEMA IADCZ	23-55				
PHEMA IADH8	203-323				
PHEMA IADNZ	23-55				
PHEMA IAFPR	18-61				
PHEMA IAGRE	23-55				
PHEMA IAMAA	22-64				
PHEMA IAMAB	27-59				
PHEMA IARUD	23-55				
PHEMA IASE2	23-55				
PHEMA IASTA	517-547				
PHEMA MUMPM	18-52	101-132			
PHEMA MUMPR	18-52	101-132			
PHEMA MUMPS	18-52	101-132			
PHEMA NDVA	80-88				
PHEMA NDVB	80-88				
PHEMA NDVD	80-88				
PHEMA NDVH	80-88				
PHEMA NDVI	80-88				

PHEMA NDVM	60-88						
PHEMA NDVO	60-88						
PHEMA NDVTG	60-88						
PHEMA NDVU	60-88						
PHEMA PI1HW	29-80	198-233					
PHEMA PI2H	13-48	334-389					
PHEMA PI2HT	13-48	334-389					
PHEMA PI3B	194-231						
PHEMA PI3H4	194-231						
PHEMA PI3HA	194-231						
PHEMA PI3HT	194-231						
PHEMA PI3HU	194-231						
PHEMA PI3HV	194-231						
PHEMA PI3HW	194-231						
PHEMA PI3HX	194-231						
PHEMA PI4HA	245-280	338-376					
PHEMA PI4VI	255-283						
PHEMA RINDL	282-313						
PHEMA SEND6	18-54	198-233					
PHEMA SENDF	18-54	198-233					
PHEMA SENDH	18-54	198-233					
PHEMA SENDJ	18-54	198-233					
PHEMA SENDZ	23-54	198-233					
PHEMA 8VA1	55-84	330-365					
PHEMA 8VB	7-35						
PHEMA 8V6CM	7-41						
PHEMA 8V6CP	7-41						
PHEMA 8V6LN	7-35						
PHEMA VACCC	258-284						
PHEMA VACCI	258-284						
PHEMA VACCT	258-284						
PHEMA VACCV	258-284						
PVENV BEV	18-51	87-117					
PVENV DHV1	287-335						
PVENV MCV1	203-238						
PVENV MCV2	203-238						
PVENV VACCC	208-241						
PVENV VACCI	208-241						
PVENV VACCP	208-241						
PVENV VACCV	208-241						
PVF03 VACCC	2-40	61-93					
PVF03 VACCV	2-40	61-93					
PVF01 FOWPV	287-330						
PVF04 FOWPV	237-287						
PVF07 CAPVK	69-118						
PVF08 VACCC	28-61						
PVF08 VACCV	28-61						

PVG01 HSV11	317-340				
PVG02 HSVB	163-186				
PVG02 VACCV	92-120				
PVG02 VARV	92-120				
PVG03 HSV11	108-138				
PVG06 HSV11	64-83				
PVG06 VACCC	88-138				
PVG06 VARV	88-138				
PVG07 VACCC	113-145				
PVG07 VARV	113-145				
PVG08 VACCC	303-338				
PVG08 VACCV	288-301				
PVG08 VARV	303-338				
PVG11 HSV11	150-183				
PVG12 HSV11	208-243				
PVG12 HSVB	88-106				
PVG1 8PV1R	254-282	303-337	414-462		
PVG22 HSV11	300-337	647-678			
PVG23 HSV11	70-108				
PVG26 HSV11	94-125				
PVG27 HSVB	38-74				
PVG28 HSV11	481-521				
PVG28 HSVB	7-40				
PVG2R AMEPV	180-217				
PVG2 8PV4	208-244				
PVG35 HSV11	18-46	180-228			
PVG38 HSVB	151-185				
PVG39 HSV11	543-577	848-882			
PVG40 HSVB	187-216				
PVG41 HSV11	11-46	202-233			
PVG42 HSV11	81-125				
PVG43 HSV11	108-140	167-185			
PVG48 HSV11	888-926				
PVG48 HSVB	328-357				
PVG50 HSVB	113-141				
PVG81 HSV11	28-64	84-120			
PVG82 HSV11	88-134				
PVG85 HSV11	100-129				
PVG86 HSV11	631-667	1081-1128			
PVG88 HSV11	342-376	480-508			
PVG89 HSVB	28-80	196-233			
PVG89 HSV11	82-118				
PVG81 HSV11	78-108				
PVG84 HSV11	65-88	363-401	420-452		
PVG85 HSV11	601-838	1280-1328			
PVG87 HSV11	150-188	1160-1185			
PVG8 8PV1R	60-89				

PVQ71 H8V8A	128-168				
PVQ72 H8V11	446-478	720-781	1168-1189	1262-1286	
PVQ76 H8V11	283-291	387-422			
PVQ78 H8V11	187-221				
PVQ7 8PV1R	18-48				
PVQF1 IBVB	1718-1747	1856-1881	2108-2148	3801-3833	
PVQH3 HCMVA	80-116	187-188			
PVQ12 CVBPF	1259-1284				
PVQ12 CVBL0	681-681	1259-1294			
PVQ12 CVBLY		1259-1294			
PVQ12 CVBM		1259-1294			
PVQ12 CVBQ		1259-1294			
PVQ12 CVBV		1259-1294			
PVQ12 CVH22	1063-1088				
PVQ12 CVH4	1267-1304				
PVQ12 CVMA5	1216-1262				
PVQ12 CVMAH	1126-1183				
PVQ12 CVPF8	632-666	738-764	1328-1363		
PVQ12 CVPPU	630-663	734-762	1328-1381		
PVQ12 CVPR8	612-640	1104-1138			
PVQ12 CVPRM	408-441	1104-1138			
PVQ12 PIPV	835-868	738-767	1331-1368		
PVQ12 IBVB	153-188				
PVQ18 HCMVA	116-147	708-743			
PVQ18 HCMVT	116-147	707-744			
PVQ18 H8VB0	72-110				
PVQ18 H8VB1	264-288				
PVQ18 H8VB2	264-288	745-774			
PVQ18 H8V8C	263-287				
PVQ18 LTV8	442-472				
PVQ18 LTV8	482-482				
PVQ18 LTVT	482-482				
PVQ18 MCMV8	136-183	738-778			
PVQ18 H8V11	487-500				
PVQ18 H8V1K	487-500				
PVQ18 H8V2	435-465				
PVQ18 H8V23	436-466				
PVQ18 H8V8C	476-607				
PVQ18 VZVD	351-388	513-548			
PVQ18 VZVB	351-388	513-548			
PVQ18 H8VEA	340-370				
PVQ18 H8VEB	41-70	380-420			
PVQ18 H8VEK	41-70	390-420			
PVQ18 H8VE4	86-126				
PVQ18 H8VEB	63-100	380-420			
PVQ18 H8VEL	63-100	382-422			
PVQ18 PRV1	332-369				

PVQLF BR8VA	205-301	482-511		
PVQLF BR8VC	484-513			
PVQLF BR8VR	484-513			
PVQLF CDVO	682-888			
PVQLF HRSV1	484-513			
PVQLF HRSVA	484-513			
PVQLF HRSVL	484-513			
PVQLF HRSVR	484-513			
PVQLF MEASE	224-258	451-484		
PVQLF MEABI	227-258	454-487		
PVQLF MEASY	224-258	451-484		
PVQLF MUMPM	448-474			
PVQLF MUMPR	448-474			
PVQLF MUMPS	5-38	445-474		
PVQLF NDVI	132-185			
PVQLF PHODV	531-555			
PVQLF PI1HC	458-484			
PVQLF PI3B	453-481			
PVQLF PI3H4	453-481			
PVQLF RINDK	220-252	447-480		
PVQLF RINDL	220-252	447-480		
PVQLF SEND5	450-488			
PVQLF SENDF	480-488			
PVQLF SENDH	480-488			
PVQLF SENDJ	480-488			
PVQLF SENDZ	480-488			
PVQLF SV6	448-474			
PVQLF TRTV	452-481			
PVQLG H8VEB	327-384			
PVQLG SYNV	524-553			
PVQLG V8VIQ	450-488			
PVQLG V8VJO	457-492			
PVQLG V8VO	450-488			
PVQLG V8V6J	450-488			
PVQLH HCMVA	601-718			
PVQLH HCMVT	690-718			
PVQLH H8V6G	640-677			
PVQLH H8VE4	814-850			
PVQLH H8VEB	807-843			
PVQLI HCMVA	158-184			
PVQLM BUNGE	197-227	438-468	882-1020	1048-1084
PVQLM BUNL7	180-220			
PVQLM BUNSH	190-220	344-381		
PVQLM BUNYW	183-228	434-472	823-854	
PVQLM DUGBV	244-273	637-672	888-918	935-985
PVQLM HANTB	610-641	1081-1119		1403-1441
PVQLM HANTH	188-222	612-643	1082-1120	

PVGLM HANTL	188-222	812-843	1083-1121	
PVGLM HANTV	188-222	812-843	1083-1121	
PVGLM PHV	616-848	1088-1121		
PVGLM PTPV	848-982	1276-1308		
PVGLM PUUMH	620-853	1092-1128		
PVGLM PUUMS	620-853	1092-1128		
PVGLM RVFV	620-853	830-863		
PVGLM RVFVZ	620-853	830-863	1168-1186	
PVGLM SEOUR	606-841	1082-1120		
PVGLM SEOUR	610-841	1091-1119		
PVGLM UUK	431-488	986-986		
PVGLP BEV	1491-1528			
PVGLY JUNIN	12-45			
PVGLY LASSQ	237-268			
PVGLY LASSJ	238-268			
PVGLY PIARV	12-60			
PVGLY TACV	12-60			
PVGLY TACV6	12-60	88-124		
PVGLY TACV7	12-60	88-124		
PVGLY TACVT	12-60	88-124		
PVGLB CPMV	1527-1555			
PVGLN BPMV	137-187	280-327	837-868	
PVGLN CPMV	208-242	741-771		
PVGLN CPMV	50-88	478-515		
PVGLN RCMV	768-789			
PVGP2 EBV	78-111			
PVGP3 EBV	78-111			
PVM1 REOVD	280-318	324-381		
PVM1 REOVL	280-318			
PVM21 REOVD	188-188			
PVM22 REOVD	188-188			
PVM2 REOVL	188-188			
PVM2 REOVL	188-188			
PVM3 REOVD	333-384			
PVMAT 8V6	308-342			
PVMAT TRTV	122-180			
PVME1 CVBM	64-102			
PVME1 CVHOC	64-102			
PVME1 CVMA6	66-103			
PVME1 CVMAH	66-103			
PVME1 CVTRK	64-102			
PVME1 EBV	178-213			
PVMP CERV	93-126			
PVMP 6OCMV	68-98	273-303		
PVMSA HPBDB	201-238	288-302		
PVMSA HPBDC	184-227	288-301		
PVMSA HPBDU	157-180	231-264		

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5.3. SYNTHESIS OF PEPTIDES

The peptides of the invention may be synthesized or prepared by techniques well known in the art. See, for example, Creighton, 1983, *Proteins: Structures and Molecular Principles*, W.H. Freeman and Co., NY, which is incorporated herein by reference in its entirety. Short peptides, for example, can be synthesized on a solid support or in solution. Longer peptides may be made using recombinant DNA techniques. Here, the nucleotide sequences encoding the peptides of the invention may be synthesized, and/or cloned, and expressed according to techniques well known to those of ordinary skill in the art. See, for example, Sambrook, et al., 1989, *Molecular Cloning, A Laboratory Manual*, Vols. 1-3, Cold Spring Harbor Press, NY.

The peptides of the invention may alternatively be synthesized such that one or more of the bonds which link the amino acid residues of the peptides are non-peptide bonds. These alternative non-peptide bonds may be formed by utilizing reactions well known to those in the art, and may include, but are not limited to imino, ester, hydrazide, semicarbazide, and azo bonds, to name but a few. In yet another embodiment of the invention, peptides comprising the sequences described above may be synthesized with additional chemical groups present at their amino and/or carboxy termini, such that, for example, the stability, bioavailability, and/or inhibitory activity of the peptides is enhanced. For example, hydrophobic groups such as carbobenzoxy, dansyl, or t-butyloxycarbonyl groups, may be added to the peptides' amino termini. Likewise, an acetyl group or a 9-fluorenylmethoxy-carbonyl group may be placed at the peptides' amino termini. (See "X" in Tables I to IV, above.) Additionally, the hydrophobic group, t-

butyloxycarbonyl, or an amido group may be added to the peptides' carboxy termini. (See "Z" in Tables I to IV, above.) Further, the peptides of the invention may be synthesized such that their steric configuration is altered. For example, the D-isomer
5 of one or more of the amino acid residues of the peptide may be used, rather than the usual L-isomer. Still further, at least one of the amino acid residues of the peptides of the invention may be substituted by one of the well known non-naturally occurring amino
10 acid residues. Alterations such as these may serve to increase the stability, bioavailability and/or inhibitory action of the peptides of the invention.

Any of the peptides described above may, additionally, have a non-peptide macromolecular
15 carrier group covalently attached to their amino and/or carboxy termini. Such macromolecular carrier groups may include, for example, lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates. "X", in Tables I to IV, above, may therefore
20 additionally represent any of the above macromolecular carrier groups covalently attached to the amino terminus of a peptide. Likewise, "Z", in Tables I to IV, may additionally represent any of the
25 macromolecular carrier groups described above.

5.4. ASSAYS FOR ANTIVIRAL ACTIVITY

The antiviral activity exhibited by the peptides of the invention may be measured, for example, by easily performed in vitro assays, such as those
30 described below, which can test the peptides' ability to inhibit syncytia formation, or their ability to inhibit infection by cell-free virus. Using these assays, such parameters as the relative antiviral activity of the peptides, exhibit against a given
35 strain of virus and/or the strain specific inhibitory

activity of the peptide can be determined. A cell fusion assay may be utilized to test the peptides' ability to inhibit HIV-induced syncytia formation in vitro. Such an assay may comprise culturing uninfected CD-4⁺ cells (such as Molt or CEM cells, for example) in the presence of chronically HIV-infected cells and a peptide to be assayed. For each peptide, a range of peptide concentrations may be tested. This range should include a control culture wherein no peptide has been added. Standard conditions for culturing, well known to those of ordinary skill in the art, are used. After incubation for an appropriate period (24 hours at 37°C, for example) the culture is examined microscopically for the presence of multinucleated giant cells, which are indicative of cell fusion and syncytia formation.

A reverse transcriptase (RT) assay may be utilized to test the peptides' ability to inhibit infection of CD-4⁺ cells by cell-free HIV. Such an assay may comprise culturing an appropriate concentration (i.e., TCID₅₀) of virus and CD-4⁺ cells in the presence of the peptide to be tested. Culture conditions well known to those in the art are used. As above, a range of peptide concentrations may be used, in addition to a control culture wherein no peptide has been added. After incubation for an appropriate period (e.g., 7 days) of culturing, a cell-free supernatant is prepared, using standard procedures, and tested for the presence of RT activity as a measure of successful infection. The RT activity may be tested using standard techniques such as those described by, for example, Goff et al. (Goff, S. et al., 1981, J. Virol. 38:239-248) and/or Willey et al. (Willey, R. et al., 1988, J. Virol. 62:139-147). These references are incorporated herein by reference in their entirety.

Standard methods which are well-known to those of skill in the art may be utilized for assaying non-retroviral activity. See, for example, Pringle et al. (Pringle, C.R. et al., 1985, J. Medical Virology 17:377-386) for a discussion of respiratory syncytial virus and parainfluenza virus activity assay techniques. Further, see, for example, "Zinsser Microbiology", 1988, Joklik, W.K. et al., eds., Appleton & Lange, Norwalk, CT, 19th ed., for a general review of such techniques. These references are incorporated by reference herein in its entirety.

5.5. USES OF THE PEPTIDES OF THE INVENTION

The DP-178 (SEQ ID:1) peptides of the invention, and DP-178 fragments, analogs, and homologs, exhibit potent antiviral activity. The DP-107-like and DP-178-like peptides of the invention preferably exhibit antiviral activity. As such, the peptides may be used as inhibitors of human and non-human viral and retroviral, especially HIV, transmission to uninfected cells.

The human retroviruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to all strains of HIV-1 and HIV-2 and the human T-lymphocyte viruses (HTLV-I and II). The non-human retroviruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to bovine leukosis virus, feline sarcoma and leukemia viruses, simian immunodeficiency, sarcoma and leukemia viruses, and sheep progress pneumonia viruses.

Non retroviral viruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to human respiratory syncytial virus, canine distemper virus, newcastle disease virus, human parainfluenza virus, and influenza

viruses. Further, any virus or retrovirus containing peptides listed in Tables V through X above, may be inhibited by the peptides of the invention.

As discussed more fully, below, in Section 5.5.1 and in the Example presented, below, in Section 8, DP-107 and DP-178, and DP-107-like and DP-178-like peptides form non-covalent protein-protein interactions which are required for normal activity of the virus. Thus, the peptides of the invention may also be utilized as components in assays for the identification of compounds that interfere with such protein-protein interactions and may, therefore, act as antiviral agents. These assays are discussed, below, in Section 5.5.1.

5.5.1. ANTIVIRAL COMPOUND SCREENING ASSAYS FOR COMPOUNDS THAT INTERACT WITH THE PKD1 GENE PRODUCT

As demonstrated in the Example presented in Section 8, below, DP-107 and DP-178 portions of the TM protein gp41 form non-covalent protein-protein interactions. As also demonstrated, the maintenance of such interactions is necessary for normal viral infectivity. Thus, compounds which bind DP-107, bind DP-178, and/or act to disrupt normal DP-107/DP-178 protein-protein interactions may act as potent antiviral agents. Described below are assays for the identification of such compounds. Note that, while, for ease and clarity of discussion, DP-107 and DP-178 peptides will be used as components of the assays described, but it is to be understood that any of the DP-107-like or DP-178-like peptides described, above, in Sections 5.1 and 5.2 may also be utilized as part of these screens for antiviral compounds.

Compounds which may be tested for an ability to bind DP-107, DP-178, and/or disrupt DP-107/DP-178 interactions, and which therefore, potentially

represent antiviral compounds, include, but are not limited to, peptides made of D- and/or L-configuration amino acids (in, for example, the form of random peptide libraries; see Lam, K.S. *et al.*, 1991, *Nature* 354:82-84), phosphopeptides (in, for example, the form of random or partially degenerate, directed phosphopeptide libraries; see, for example, Songyang, Z. *et al.*, 1993, *Cell* 72:767-778), antibodies, and small organic or inorganic molecules. Synthetic compounds, natural products, and other sources of potentially effective materials may be screened in a variety of ways, as described in this Section. The compounds, antibodies, or other molecules identified may be tested for an ability to inhibit viral activity, utilizing, for example, viral assays such as those described, above, in Section 5.4.

Among the peptides which may be tested are soluble peptides comprising DP-107 and/or DP-178 domains, and peptides comprising DP-107 and/or DP-178 domains having one or more mutations within one or both of the domains, such as the M41-P peptide described, below, in the Example presented in Section 8, which contains a isoleucine to proline mutation within the DP-178 sequence.

In one embodiment of such screening methods is a method for identifying a compound to be tested for antiviral ability comprising:

- (a) exposing at least one compound to a peptide comprising a DP-107 peptide for a time sufficient to allow binding of the compound to the DP-107 peptide;
- (b) removing non-bound compounds; and
- (c) determining the presence of the compound bound to the DP-107 peptide, thereby identifying an agent to be tested for antiviral ability.

In a second embodiment of such screening methods is a method for identifying a compound to be tested for antiviral ability comprising:

- (a) exposing at least one compound to a peptide comprising a DP-178 peptide for a time
5 sufficient to allow binding of the compound to the DP-178 peptide;
- (b) removing non-bound compounds; and
- (c) determining the presence of the
10 compound bound to the DP-178 peptide,
thereby identifying an agent to be tested for
antiviral ability.

One method utilizing these types of approaches that may be pursued in the isolation of such DP-107-binding or DP-178-binding compounds is an assay which
15 would include the attachment of either the DP-107 or the DP-178 peptide to a solid matrix, such as, for example, agarose or plastic beads, microtiter plate wells, petri dishes, or membranes composed of, for example, nylon or nitrocellulose. In such an assay
20 system, either the DP-107 or DP-178 protein may be anchored onto a solid surface, and the compound, or test substance, which is not anchored, is labeled, either directly or indirectly. In practice, microtiter plates are conveniently utilized. The
25 anchored component may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished simply by coating the solid surface with a solution of the protein and drying. Alternatively, an immobilized antibody, preferably a
30 monoclonal antibody, specific for the protein may be used to anchor the protein to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the labeled
35 compound is added to the coated surface containing the anchored DP-107 or DP-178 peptide. After the reaction

is complete, unreacted components are removed (e.g., by washing) under conditions such that any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways.

5 Where the compound is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the labeled component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using
10 a labeled antibody specific for the compound (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody).

Alternatively, such an assay can be conducted in a liquid phase, the reaction products separated from
15 unreacted components, and complexes detected; e.g., using an immobilized antibody specific for DP-107 or DP-178, whichever is appropriate for the given assay, or an antibody specific for the compound, i.e., the test substance, in order to anchor any complexes
20 formed in solution, and a labeled antibody specific for the other member of the complex to detect anchored complexes.

By utilizing procedures such as this, large numbers of types of molecules may be simultaneously
25 screened for DP-107 or DP-178-binding capability, and thus potential antiviral activity.

Further, compounds may be screened for an ability to inhibit the formation of or, alternatively, disrupt DP-107/DP-178 complexes. Such compounds may then be
30 tested for antiviral capability. For ease of description, DP-107 and DP-178 will be referred to as "binding partners." Compounds that disrupt such interactions may exhibit antiviral activity. Such compounds may include, but are not limited to

35

molecules such as antibodies, peptides, and the like described above.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the DP-107 and DP-178 peptides involves
5 preparing a reaction mixture containing peptides under conditions and for a time sufficient to allow the two peptides to interact and bind, thus forming a complex. In order to test a compound for disruptive activity, the reaction is conducted in the presence and absence
10 of the test compound, i.e., the test compound may be initially included in the reaction mixture, or added at a time subsequent to the addition of one of the binding partners; controls are incubated without the test compound or with a placebo. The formation of any
15 complexes between the binding partners is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound indicates that the compound interferes with the interaction of the DP-107 and
20 DP-178 peptides.

The assay for compounds that interfere with the interaction of the binding partners can be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring one of the
25 binding partners onto a solid phase and detecting complexes anchored on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be
30 varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the binding partners, e.g., by competition, can be identified by conducting the reaction in the presence
35 of the test substance; i.e., by adding the test

substance to the reaction mixture prior to r
simultaneously with the binding partners. On the
ther hand, test compounds that disrupt preformed
complexes, e.g. compounds with higher binding
constants that displace one of the binding partners
5 from the complex, can be tested by adding the test
compound to the reaction mixture after complexes have
been formed. The various formats are described
briefly below.

10 In a heterogeneous assay system, one binding
partner, e.g., either the DP-107 or DP-178 peptide, is
anchored onto a solid surface, and its binding
partner, which is not anchored, is labeled, either
directly or indirectly. In practice, microtiter
15 plates are conveniently utilized. The anchored
species may be immobilized by non-covalent or covalent
attachments. Non-covalent attachment may be
accomplished simply by coating the solid surface with
a solution of the protein and drying. Alternatively,
20 an immobilized antibody specific for the protein may
be used to anchor the protein to the solid surface.
The surfaces may be prepared in advance and stored.

In order to conduct the assay, the binding
partner of the immobilized species is added to the
coated surface with or without the test compound.
25 After the reaction is complete, unreacted components
are removed (e.g., by washing) and any complexes
formed will remain immobilized on the solid surface.
The detection of complexes anchored on the solid
surface can be accomplished in a number of ways.
30 Where the binding partner was pre-labeled, the
detection of label immobilized on the surface
indicates that complexes were formed. Where the
binding partner is not pre-labeled, an indirect label
can be used to detect complexes anchored on the
35 surface; e.g., using a labeled antibody specific for

the binding partner (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which inhibit complex formation or which disrupt preformed
5 complexes can be detected.

Alternatively, the reaction can be conducted in a liquid phase in the presence or absence of the test compound, the reaction products separated from unreacted components, and complexes detected; e.g.,
10 using an immobilized antibody specific for one binding partner to anchor any complexes formed in solution, and a labeled antibody specific for the other binding partner to detect anchored complexes. Again, depending upon the order of addition of reactants to
15 the liquid phase, test compounds which inhibit complex or which disrupt preformed complexes can be identified.

In an alternate embodiment of the invention, a homogeneous assay can be used. In this approach, a
20 preformed complex of the DP-107 and DP-178 peptides is prepared in which one of the binding partners is labeled, but the signal generated by the label is quenched due to complex formation (see, e.g., U.S. Patent No. 4,109,496 by Rubenstein which utilizes this
25 approach for immunoassays). The addition of a test substance that competes with and displaces one of the binding partners from the preformed complex will result in the generation of a signal above background. In this way, test substances which disrupt DP-107/
30 DP-178 protein-protein interaction can be identified.

5.5 PHARMACEUTICAL FORMULATIONS, DOSAGES AND MODES OF ADMINISTRATION

With respect to HIV, the peptides of the
35 invention may be used as a therapeutic in the

treatment of AIDS. The peptides of the invention may be administered using techniques well known to those in the art. Preferably, agents are formulated and administered systemically. Techniques for formulation and administration may be found in "Remington's
5 Pharmaceutical Sciences", 18th ed., 1990, Mack Publishing Co., Easton, PA. Suitable routes may include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including
10 intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few. Most preferably, administration is intravenous. For injection, the agents of the invention may be
15 formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated
20 are used in the formulation. Such penetrants are generally known in the art.

In addition, the peptides may be used as a prophylactic measure in previously uninfected individuals after acute exposure to an HIV virus.
25 Examples of such prophylactic use of the peptides may include, but are not limited to, prevention of virus transmission from mother to infant and other settings where the likelihood of HIV transmission exists, such as, for example, accidents in health care settings
30 wherein workers are exposed to HIV-containing blood products. The peptides of the invention in such cases may serve the role of a prophylactic vaccine, wherein the host raises antibodies against the peptides of the invention, which then serve to neutralize HIV viruses
35 by, for example, inhibiting further HIV infection.

Administration of the peptides of the invention as a prophylactic vaccine, therefore, would comprise administering to a host a concentration of peptides effective in raising an immune response which is sufficient to neutralize HIV, by, for example, inhibiting HIV ability to infect cells. The exact concentration will depend upon the specific peptide to be administered, but may be determined by using standard techniques for assaying the development of an immune response which are well known to those of ordinary skill in the art. The peptides to be used as vaccines are usually administered intramuscularly.

The peptides may be formulated with a suitable adjuvant in order to enhance the immunological response. Such adjuvants may include, but are not limited to mineral gels such as aluminum hydroxide; surface active substances such as lysolecithin, pluronic polyols, polyanions; other peptides; oil emulsions; and potentially useful human adjuvants such as BCG and Corynebacterium parvum. Many methods may be used to introduce the vaccine formulations described here. These methods include but are not limited to oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, and intranasal routes.

Alternatively, an effective concentration of polyclonal or monoclonal antibodies raised against the peptides of the invention may be administered to a host so that no uninfected cells become infected by HIV. The exact concentration of such antibodies will vary according to each specific antibody preparation, but may be determined using standard techniques well known to those of ordinary skill in the art. Administration of the antibodies may be accomplished using a variety of techniques, including, but not limited to those described in this section.

Effective dosages of the peptides of the invention to be administered may be determined through procedures well known to those in the art which address such parameters as biological half-life, bioavailability, and toxicity. Given the data
5 presented below in Section 6, DP-178, for example, may prove efficacious in vivo at doses required achieve circulating levels of 10ng per ml of peptide.

A therapeutically effective dose refers to that amount of the compound sufficient to result in
10 amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50
15 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds
20 which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of
25 circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the
30 therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which
35 achieves a half-maximal disruption of the PTK/adaptor

prot in complex, or a half-maximal inhibition of the cellular level and/or activity of a complex component) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for
5 example, by high performance liquid chromatography (HPLC).

The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl
10 et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p1).

It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity, or to organ
15 dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the oncogenic disorder of interest
20 will vary with the severity of the condition to be treated and to the route of administration. The dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that
25 discussed above may be used in veterinary medicine.

As demonstrated in the Example presented below in Section 6, the antiviral activity of the peptides of the invention may show a pronounced type and subtype specificity, i.e., specific peptides may be effective
30 in inhibiting the activity of only specific viruses. This feature of the invention presents many advantages. One such advantage, for example, lies in the field of diagnostics, wherein one can use the antiviral specificity of the peptide of the invention
35 to ascertain the identity of a viral isolate. With

respect to HIV, one may easily determine whether a viral isolate consists of an HIV-1 or HIV-2 strain. For example, uninfected CD-4⁺ cells may be co-infected with an isolate which has been identified as containing HIV the DP-178 (SEQ ID:1) peptide, after
5 which the retroviral activity of cell supernatants may be assayed, using, for example, the techniques described above in Section 5.2. Those isolates whose retroviral activity is completely or nearly completely inhibited contain HIV-1. Those isolates whose viral
10 activity is unchanged or only reduced by a small amount, may be considered to not contain HIV-1. Such an isolate may then be treated with one or more of the other DP-178 peptides of the invention, and subsequently be tested for its viral activity in order
15 to determine the identity of the viral isolate.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the
20 invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be
25 formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups,
30 slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective
35 amount to achieve its intended purpose. Determination

of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable
5 pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated
10 for oral administration may be in the form of tablets, dragees, capsules, or solutions.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing,
15 dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active
20 compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes.
25 Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the
30 solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid
35 excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding

suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

35

6. EXAMPLE: DP-178 (SEQ ID:1) IS A POTENT
INHIBITOR OF HIV-1 INFECTION

In this example, DP-178 (SEQ ID:1) is shown to be a potent inhibitor of HIV-1 mediated CD-4⁺ cell-cell fusion and infection by cell free virus. In the fusion assay, this peptide completely blocks virus induced syncytia formation at concentrations of from 1-10 ng/ml. In the infectivity assay the inhibitory concentration is somewhat higher, blocking infection at 90ng/ml. It is further shown that DP-178 (SEQ ID:1) shows that the antiviral activity of DP-178 (SEQ ID:1) is highly specific for HIV-1. Additionally, a synthetic peptide, DP-185 (SEQ ID:3), representing a HIV-1-derived DP-178 homolog is also found to block HIV-1-mediated syncytia formation.

15

6.1. MATERIALS AND METHODS

6.1.1. PEPTIDE SYNTHESIS

Peptides were synthesized using Fast Moc chemistry on an Applied Biosystems Model 431A peptide synthesizer. Amidated peptides were prepared using Rink resin (Advanced Chemtech) while peptides containing free carboxy termini were synthesized on Wang (p-alkoxy-benzyl-alcohol) resin (Bachem). First residues were double coupled to the appropriate resin and subsequent residues were single coupled. Each coupling step was followed by acetic anhydride capping. Peptides were cleaved from the resin by treatment with trifluoroacetic acid (TFA) (10ml), H₂O (0.5ml), thioanisole (0.5ml), ethanedithiol (0.25ml), and crystalline phenol (0.75g). Purification was carried out by reverse phase HPLC. Approximately 50mg samples of crude peptide were chromatographed on a Waters Delta Pak C18 column (19mm x 30cm, 15μ spherical) with a linear gradient; H₂O/acetonitrile

0.1% TFA. Lyophilized peptides were stored desiccated and peptide solutions were made in water at about 1mg/ml. Electrospray mass spectrometry yielded the following results: DP-178 (SEQ ID:1):4491.87 (calculated 4491.94); DP-180 (SEQ ID:2):4491.45 (calculated 4491.94); DP-185 (SEQ ID:3):not done (calculated 4546.97).

6.1.2. VIRUS

The HIV-1_{LA1} virus was obtained from R. Gallo (Popovic, M. et al., 1984, Science 224:497-508) and propagated in CEM cells cultured in RPMI 1640 containing 10% fetal calf serum. Supernatant from the infected CEM cells was passed through a 0.2µm filter and the infectious titer estimated in a microinfectivity assay using the AA5 cell line to support virus replication. For this purpose, 25µl of serial diluted virus was added to 75µl AA5 cells at a concentration of 2×10^5 /ml in a 96-well microtitre plate. Each virus dilution was tested in triplicate. Cells were cultured for eight days by addition of fresh medium every other day. On day 8 post infection, supernatant samples were tested for virus replication as evidenced by reverse transcriptase activity released to the supernatant. The TCID₅₀ was calculated according to the Reed and Muench formula (Reed, L.J. et al., 1938, Am. J. Hyg. 27:493-497). The titer of the HIV-1_{LA1} and HIV-1_{MN} stocks used for these studies, as measured on the AA5 cell line, was approximately 1.4×10^6 and 3.8×10^4 TCID₅₀/ml, respectively.

6.1.3. CELL FUSION ASSAY

Approximately 7×10^4 Molt cells were incubated with 1×10^4 CEM cells chronically infected with the HIV-1_{LA1} virus in 96-well plates (one-half area cluster plates; Costar, Cambridge, MA) in a final volume of

100 μ l culture medium as previously described
(Matthews, T.J. et al., 1987, Proc. Natl. Acad. Sci.
USA 84: 5424-5428). Peptide inhibitors were added in
a volume of 10 μ l and the cell mixtures were incubated
for 24 hr. at 37°C. At that time, multinucleated
5 giant cells were estimated by microscopic examination
at a 40x magnification which allowed visualization of
the entire well in a single field.

6.1.4. CELL FREE VIRUS INFECTION ASSAY

10 Synthetic peptides were incubated at 37°C with
either 247 TCID₅₀ (for experiment depicted in FIG. 2),
or 62 TCID₅₀ (for experiment depicted in FIG.3) units
of HIV-1_{LAI} virus or 25 TCID₅₀ units of HIV-2_{NH2} and CEM
CD4⁺ cells at peptide concentrations of 0, 0.04, 0.4,
15 4.0, and 40 μ g/ml for 7 days. The resulting reverse
transcriptase (RT) activity in counts per minute was
determined using the assay described, below, in
Section 6.1.5. See, Reed, L.J. et al., 1938, Am. J.
Hyg. 27: 493-497 for an explanation of TCID₅₀
20 calculations.

6.1.5. REVERSE TRANSCRIPTASE ASSAY

The micro-reverse transcriptase (RT) assay was
adapted from Goff et al. (Goff, S. et al., 1981, J.
25 Virol. 38:239-248) and Willey et al. (Willey, R. et
al., 1988, J. Virol. 62:139-147). Supernatants from
virus/cell cultures are adjusted to 1% Triton-X100. A
10 μ l sample of supernatant was added to 50 μ l of RT
cocktail in a 96-well U-bottom microtitre plate and
30 the samples incubated at 37°C for 90 min. The RT
cocktail contained 75mM KCl, 2mM dithiothreitol, 5mM
MgCl₂, 5 μ g/ml poly A (Pharmacia, cat. No. 27-4110-01),
0.25 units/ml oligo dT (Pharmacia, cat. No. 27-7858-
01), 0.05% NP40, 50mM Tris-HCl, pH 7.8, 0.5 μ M non-
35

radioactive dTTP, and $10\mu\text{Ci/ml}$ ^{32}P -dTTP (Amersham, cat. No. PB.10167).

After the incubation period, $40\mu\text{l}$ of reaction mixture was applied to a Schleicher and Schuell (S+S) NA45 membrane (or DE81 paper) saturated in 2 x SSC buffer (0.3M NaCl and 0.003M sodium citrate) held in a S+S Minifold over one sheet of GB003 (S+S) filter paper, with partial vacuum applied. Each well of the minifold was washed four times with $200\mu\text{l}$ 2xSSC, under full vacuum. The membrane was removed from the minifold and washed 2 more times in a pyrex dish with an excess of 2xSSC. Finally, the membrane was drained on absorbent paper, placed on Whatman #3 paper, covered with Saran wrap, and exposed to film overnight at -70°C .

6.2. RESULTS

6.2.1. PEPTIDE INHIBITION OF INFECTED CELL-INDUCED SYNCYTIA FORMATION

The initial screen for antiviral activity assayed peptides' ability to block syncytium formation induced by overnight co-cultivation of uninfected Molt4 cells with chronically HIV-1 infected CEM cells. The results of several such experiments are presented herein. In the first of these experiments, serial DP-178 (SEQ ID:1) peptide concentrations between $10\mu\text{g/ml}$ and 12.5ng/ml were tested for blockade of the cell fusion process. For these experiments, CEM cells chronically infected with either HIV-1_{LAI}, HIV-1_{MN}, HIV-1_{RF}, or HIV-1_{SF2} virus were cocultivated overnight with uninfected Molt 4 cells. The results (FIG. 4) show that DP-178 (SEQ ID:1) afforded complete protection against each of the HIV-1 isolates down to the lowest concentration of DP-178 (SEQ ID:1) used. For HIV_{LAI} inhibition, the lowest concentration tested was

12.5ng/ml; for all other HIV-1 viruses, the lowest concentration of DP-178 (SEQ ID:1) used in this study was 100ng/ml. A second peptide, DP-180 (SEQ ID:2), containing the same amino acid residues as DP-178 (SEQ ID:1) but arranged in a random order exhibited no evidence of anti-fusogenic activity even at the high concentration of 40µg/ml (FIG. 4). These observations indicate that the inhibitory effect of DP-178 (SEQ ID:1) is primary sequence-specific and not related to non-specific peptide/protein interactions. The actual endpoint (i.e., the lowest effective inhibitory concentration) of DP-178 inhibitory action is within the range of 1-10 ng/ml.

The next series of experiments involved the preparation and testing of a DP-178 (SEQ ID:1) homolog for its ability to inhibit HIV-1-induced syncytia formation. As shown in FIG. 1, the sequence of DP-185 (SEQ ID:3) is slightly different from DP-178 (SEQ ID:1) in that its primary sequence is taken from the HIV-1_{SP2} isolate and contains several amino acid differences relative to DP-178 (SEQ ID:1) near the N terminus. As shown in FIG. 4, DP-185 (SEQ ID:3), exhibits inhibitory activity even at 312.5ng/ml, the lowest concentration tested.

The next series of experiments involved a comparison of DP-178 (SEQ ID:1) HIV-1 and HIV-2 inhibitory activity. As shown in FIG. 5, DP-178 (SEQ ID:1) blocked HIV-1-mediated syncytia formation at peptide concentrations below 1ng/ml. DP-178 (SEQ ID:1) failed, however, to block HIV-2 mediated syncytia formation at concentrations as high as 10µg/ml. This striking 4 log selectivity of DP-178 (SEQ ID:1) as an inhibitor of HIV-1-mediated cell fusion demonstrates an unexpected HIV-1 specificity in the action of DP-178 (SEQ ID:1). DP-178 (SEQ ID:1) inhibition of HIV-1-mediated cell fusion, but the

peptide's inability to inhibit HIV-2 medicated cell fusion in the same cell type at the concentrations tested provides further evidence for the high degree of selectivity associated with the antiviral action of DP-178 (SEQ ID:1).

5

6.2.2. PEPTIDE INHIBITION OF INFECTION BY CELL-FREE VIRUS

DP-178 (SEQ ID:1) was next tested for its ability to block CD-4⁺ CEM cell infection by cell free HIV-1 virus. The results, shown in FIG. 2, are from an experiment in which DP-178 (SEQ ID:1) was assayed for its ability to block infection of CEM cells by an HIV-1_{LAI} isolate. Included in the experiment were three control peptides, DP-116 (SEQ ID:9), DP-125 (SEQ ID:8), and DP-118 (SEQ ID:10). DP-116 (SEQ ID:9) represents a peptide previously shown to be inactive using this assay, and DP-125 (SEQ ID:8; Wild, C. *et al.*, 1992, Proc. Natl. Acad. Sci. USA **89**:10,537) and DP-118 (SEQ ID:10) are peptides which have previously been shown to be active in this assay. Each concentration (0, 0.04, 0.4, 4, and 40 µg/ml) of peptide was incubated with 247 TCID₅₀ units of HIV-1_{LAI} virus and CEM cells. After 7 days of culture, cell-free supernatant was tested for the presence of RT activity as a measure of successful infection. The results, shown in FIG. 2, demonstrate that DP-178 (SEQ ID:1) inhibited the de novo infection process mediated by the HIV-1 viral isolate at concentrations as low as 90ng/ml (IC₅₀=90ng/ml). In contrast, the two positive control peptides, DP-125 (SEQ ID:8) and DP-118 (SEQ ID:10), had over 60-fold higher IC₅₀ concentrations of approximately 5 µg/ml.

In a separate experiment, the HIV-1 and HIV-2 inhibitory action of DP-178 (SEQ ID:1) was tested with CEM cells and either HIV-1_{LAI} or HIV-2_{NIH2}. 62 TCID₅₀

HIV-1_{LAI} or 25 GCID₅₀ HIV-2_{NIH} were used in these experiments, and were incubated for 7 days. As may be seen in FIG. 3, DP-178 (SEQ ID:1) inhibited HIV-1 infection with an IC₅₀ of about 31ng/ml. In contrast, DP-178 (SEQ ID:1) exhibited a much higher IC₅₀ for HIV-2_{NIH}, thus making DP-178 (SEQ ID:1) two logs more potent as a HIV-1 inhibitor than a HIV-2 inhibitor. This finding is consistent with the results of the fusion inhibition assays described, above, in Section 6.2.1, and further supports a significant level of selectivity (i.e., for HIV-1 over HIV-2).

7. EXAMPLE: THE HIV-1 INHIBITOR, DP-178 (SEQ ID:1) IS NON-CYTOXIC

In this Example, the 36 amino acid synthetic peptide inhibitor DP-178 (SEQ ID:1) is shown to be non-cytotoxic to cells in culture, even at the highest peptide concentrations (40μg/ml) tested.

7.1. MATERIALS AND METHODS

Cell proliferation and toxicity assay:
Approximately 3.8x10⁵ CEM cells for each peptide concentration were incubated for 3 days at 37°C in T25 flasks. Peptides tested were DP-178 (SEQ ID:1) and DP-116 (SEQ ID:9), as described in FIG. 1. The concentrations of each peptide used were 0, 2.5, 10, and 40μg/ml. Cell counts were taken at incubation times of 0, 24, 48, and 72 hours.

7.2. RESULTS

Whether the potent HIV-1 inhibitor DP-178 (SEQ ID:1) exhibited any cytotoxic effects was assessed by assaying the peptide's effects on the proliferation and viability of cells in culture. CEM cells were incubated in the presence of varying concentrations of DP-178 (SEQ ID:1), and DP-116 (SEQ ID:9), a peptide

previously shown to be ineffective as a HIV inhibitor (Wild, C. et al., 1992, Proc. Natl. Acad. Sci. USA 89:10,537-10,541). Additionally, cells were incubated in the absence of either peptide.

5 The results of the cytotoxicity study demonstrate that DP-178 (SEQ ID:1) exhibits no cytotoxic effects on cells in culture. As can be seen, below, in Table XI, even the proliferation and viability characteristics of cells cultured for 3 days in the presence of the highest concentration of DP-178 (SEQ
10 ID:1) tested (40 µg/ml) do not significantly differ from the DP-116 (SEQ ID:9) or the no-peptide controls. The cell proliferation data is also represented in graphic form in FIG. 6. As was demonstrated in the Working Example presented above in Section 6, DP-178
15 (SEQ ID:1) completely inhibits HIV-1 mediated syncytia formation at peptide concentrations between 1 and 10 ng/ml, and completely inhibits cell-free viral infection at concentrations of at least 90 ng/ml. Thus, this study demonstrates that even at peptide
20 concentrations greater than 3 log higher than the HIV inhibitory dose, DP-178 (SEQ ID:1) exhibits no cytotoxic effects.

25 TABLE XI

Peptide	Peptide Concentration µg/ml	% Viability at time (hours)			
		0	24	48	72
30 DP178 (SEQ ID:1)	40	98	97	95	97
	10	98	97	98	98
	2.5	98	93	96	96

35

5	DP116 (SEQ ID:9)	40	98	95	98	97
		10	98	95	93	98
		2.5	98	96	98	99
	No Peptide	0	98	97	99	98

10 8. EXAMPLE: THE INTERACTION OF DP178 AND DP107
 Soluble recombinant forms of gp41 used in the
 example described below provide evidence that the
 DP178 peptide associates with a distal site on gp41
 whose interactive structure is influenced by the DP107
 15 leucine zipper motif. A single mutation disrupting
 the coiled-coil structure of the leucine zipper domain
 transformed the soluble recombinant gp41 protein from
 an inactive to an active inhibitor of HIV-1 fusion.
 This transformation may result from liberation of the
 20 potent DP178 domain from a molecular clasp with the
 leucine zipper, DP107, determinant. The results also
 indicate that the anti-HIV activity of various gp41
 derivatives (peptides and recombinant proteins) may be
 due to their ability to form complexes with viral gp41
 25 and interfere with its fusogenic process.

8.1. MATERIALS AND METHODS

8.1.1. CONSTRUCTION OF FUSION PROTEINS AND GP41 MUTANTS

30 Construction of fusion proteins and mutants shown
 in FIG. 7 was accomplished as follows: the DNA
 sequence corresponding to the extracellular domain of
 gp41 (540-686) was cloned into the Xmn I site of the
 expression vector pMal-p2 (New England Biolab) to give
 35 M41. The gp41 sequence was amplified from pgtat

(Malim et al., 1988, Nature 355: 181-183) by using polymerase chain reaction (PCR) with upstream primer 5'-ATGACGCTGACGGTACAGGCC-3' (primer A) and downstream primer 5'-TGAATAAGCTTAATACCACAGCCAATTTGTTAT-3' (primer B). M41-P was constructed by using the T7-Gen
5 in vitro mutagenesis kit from United States Biochemicals (USB) following the supplier's instructions. The mutagenic primer (5'-GGAGCTGCTTGGGGCCCCAGAC-3') introduces an Ile to Pro mutation in M41 at position 578. M41Δ107 was made
10 using a deletion mutagenic primer 5'-CCAAATCCCCAGGAGCTGCTCGAGCTGCACTATACCAGAC-3' (primer C) following the USB T7-Gen mutagenesis protocol. M41Δ178 was made by cloning the DNA fragment corresponding to gp41 amino acids 540-642 into the Xmn
15 I site of pMal-p2. Primer A and 5'-ATAGCTTCTAGATTAAATTGTTAATTTCTCTGTCCC-3' (primer D) were used in the PCR with the template pgtat to generate the inserted DNA fragments. M41-P was used as the template with primer A and D in PCR to generate M41-
20 PA178. All inserted sequences and mutated residues were checked by restriction enzyme analysis and confirmed by DNA sequencing.

25 8.1.2. PURIFICATION AND CHARACTERIZATION OF FUSION PROTEINS

The fusion proteins were purified according to the protocol described in the manufacturer's brochure of protein fusion and purification systems from New England Biolabs (NEB). Fusion proteins (10 ng) were
30 analyzed by electrophoresis on 8% SDS polyacrylamide gels. Western blotting analysis was performed as described by Sambrook et al, 1989, Molecular Cloning: A Laboratory Manual, 2d Ed, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, Ch. 18,
35 pp. 64-75. An HIV-1 positive serum diluted 1000-fold,

or a human Fab derived from repertoire cloning was used to react with the fusion proteins. The second antibody was HRP-conjugated goat antihuman Fab. An ECL Western blotting detection system (Amersham) was used to detect the bound antibody. A detailed
5 protocol for this detection system was provided by the manufacturer. Rainbow molecular weight marker (Amersham) were used to estimate the size of fusion proteins.

10 8.1.3. CELL FUSION ASSAYS FOR ANTI-HIV ACTIVITY

Cell fusion assays were performed as previously described (Matthews et al., 1987, Proc. Natl. Acad. Sci. USA 84: 5424-5481). CEM cells (7×10^4) were
15 incubated with HIV-1_{mb} chronically infected CEM cells (10^4) in 96-well flat-bottomed half-area plates (Costar) in 100 μ l culture medium. Peptide and fusion proteins at various concentrations in 10 μ l culture medium were incubated with the cell mixtures at 37°C for 24 hours. Multinucleated syncytia were estimated
20 with microscopic examination. Both M41 and M41-P did not show cytotoxicity at the concentrations tested and shown in FIG. 8.

Inhibition of HIV-1 induced cell-cell fusion activity was carried out in the presence of 10 nM
25 DP178 and various concentrations of M41 Δ 178 or M41-PA178 as indicated in FIG. 9. There was no observable syncytia in the presence of 10 nM DP178. No peptide or fusion protein was added in the control samples.

30 8.1.4. ELISA ANALYSIS OF DP178 BINDING TO THE LEUCINE ZIPPER MOTIF OF GP41

The amino acid sequence of DP178 used is:
YTSLIHSLEESQNQQEKNEQELLELDKWASLWNWF. For enzyme
linked immunoassay (ELISA), M41 Δ 178 or M41-PA178 (5
35 μ g/ml) in 0.1M NaHCO₃, pH 8.6, were coated on 96 wells

Linbro ELISA plates (Flow Lab, Inc.) overnight. Each well was washed three times with distilled water then blocked with 3% bovine serum albumin (BSA) for 2 hours. After blocking, peptides with 0.5% BSA in TBST (40 mM Tris-HCl pH7.5, 150 mM NaCl, 0.05% Tween 20) were added to the ELISA plates and incubated at room temperature for 1 hour. After washing three times with TBST, Fab-d was added at a concentration of 10 ng/ml with 0.5% BSA in TBST. The plates were washed three times with TBST after incubation at room temperature for 1 hour. Horse radish peroxidase (HRP) conjugated goat antihuman Fab antiserum at a 2000 fold dilution in TBST with 0.5% BSA was added to each well and incubated at room temperature for 45 minutes. The plates were then washed four times with TBST. The peroxidase substrate o-phenylene diamine (2.5 mg/ml) and 0.15% H₂O₂ were added to develop the color. The reaction was stopped with an equal volume of 4.5 N H₂SO₄ after incubation at room temperature for 10 minutes. The optical density of the stopped reaction mixture was measured with a micro plate reader (Molecular Design) at 490 nm. Results are shown in FIG. 10.

8.2. RESULTS

8.2.1. THE EXPRESSION AND CHARACTERIZATION OF THE ECTODOMAIN OF GP41

As a step toward understanding the roles of the two helical regions in gp41 structure and function, the ectodomain of gp41 was expressed as a maltose binding fusion protein (M41) (Fig. 7). The fusogenic peptide sequence at the N-terminal of gp41 was omitted from this recombinant protein and its derivatives to improve solubility. The maltose binding protein facilitated purification of the fusion proteins under relatively mild, non-denaturing conditions. Because

the M41 soluble r combinant gp41 was not glycosylated, lacked several regions of the transmembrane protein (i.e., the fusion peptid , the membrane spanning, and the cytoplasmic domains), and was expressed in the absence of gp120, it was not expected to precisely
5 reflect the structure of native gp41 on HIV-1 virions. Nevertheless, purified M41 folded in a manner that preserved certain discontinuous epitopes as evidenced by reactivity with human monoclonal antibodies, 98-6, 126-6, and 50-69, previously shown to bind
10 conformational epitopes on native gp41 expressed in eukaryotic cells (Xu et al., 1991, J. Virol. 65: 4832-4838; Chen, 1994, J. Virol. 68:2002-2010). Thus, at least certain regions of native gp41 defined by these antibodies appear to be reproduced in the recombinant
15 fusion protein M41. Furthermore, M41 reacted with a human recombinant Fab (Fab-d) that recognizes a conformational epitope on gp41 and binds HIV-1 virions as well as HIV-1 infected cells but not uninfected cells as analyzed by FACS. Deletion of either helix
20 motif, i.e., DP107 or DP178, of the M41 fusion protein eliminated reactivity with Fab-d. These results indicate that both helical regions, separated by 60 amino acids in the primary sequence, are required to maintain the Fab-d epitope.
25

8.2.2. ANTI-HIV ACTIVITY OF THE RECOMBINANT ECTODOMAIN OF GP41

The wild type M41 fusion protein was tested for
30 anti-HIV-1 activity. As explained, supra, synthetic peptides corresponding to the leucine zipper (DP107) and the C-terminal putative helix (DP178) show potent anti-HIV activity. Despite inclusion of both these regions, the recombinant M41 protein did not affect
35

HIV-1 induced membrane fusion at concentrations as high as 50 μ M (Table XII, below).

TABLE XII
DISRUPTION OF THE LEUCINE ZIPPER OF
GP41 FREES THE ANTI-HIV MOTIF

	<u>DP107</u>	<u>DP178</u>	<u>M41</u>	<u>M41-P</u>	<u>M41-PA178</u>
Cell fusion (IC ₅₀)	1 μ M	1 nM	> 50 μ M	83 nM	> 50 μ M
10 Fab-D binding (K _D)	-	-	3.5x10 ⁻⁹	2.5x10 ⁻⁸	-
HIV infectiv- ity (IC ₅₀)	1 μ M	80 nM	> 16 μ M	66 nM	> 8 μ M

The affinity constants of Fab-d binding to the fusion proteins were determined using a protocol described by B. Friguet et al., 1985, J. Immunol. Method. 77:305-319.

- = No detectable binding of Fab-d to the fusion proteins.

Antiviral Infectivity Assays. 20 μ l of serially diluted virus stock was incubated for 60 minutes at ambient temperature with 20 μ l of the indicated concentration of purified recombinant fusion protein in RPMI 1640 containing 10% fetal bovine serum and antibiotics in a 96-well microtiter plate. 20 μ l of CEM4 cells at 6 x 10⁵ cells/ml were added to each well, and cultures were incubated at 37°C in a humidified CO₂ incubator. Cells were cultured for 9 days by the addition of fresh medium every 2 to 30 days. On days 5, 7, and 9 postinfection, supernatant samples were assayed for reverse transcriptase (RT) activity, as described below, to monitor viral replication. The 50% tissue culture infectious dose (TCID₅₀) was calculated for each condition according to the formula of Reed & Muench, 1937, Am. J. Hyg. 27:493-497. RT activity was determined by a modification of the published methods of Goff et al., 1981, J. Virol. 38:239-248 and Willey et al., 1988, J. Virol. 62:139-147 as described in Chen et al., 1993, AIDS Res. Human Retroviruses 9:1079-1086.

Surprisingly, a single amino acid substitution, proline in place of isoleucine in the middle of the leucine zipper motif, yielded a fusion protein (M41-P)

which did exhibit antiviral activity (Table XII and Fig. 8). As seen in Table XII, M41-P blocked syncytia formation by 90% at approximately 85 nM and neutralized HIV-1_{MB} infection by 90% at approximately 70 nM concentrations. The anti-HIV-1 activity of M41-P appeared to be mediated by the C-terminal helical sequence since deletion of that region from M41-P yielded an inactive fusion protein, M41-PA178 (Table XII). That interpretation was reinforced by experiments demonstrating that a truncated fusion protein lacking the DP178 sequence, M41Δ178, abrogated the potent anti-fusion activity of the DP178 peptide in a concentration-dependent manner (FIG. 9). The same truncated fusion protein containing the proline mutation disrupting the leucine zipper, M41-PA178, was not active in similar competition experiments (FIG. 9). The results indicate that the DP178 peptide associates with a second site on gp41 whose interactive structure is dependent on a wild type leucine zipper sequence. A similar interaction may occur within the wild type fusion protein, M41, and act to form an intramolecular clasp which sequesters the DP178 region, making it unavailable for anti-viral activity.

A specific association between these two domains is also indicated by other human monoclonal Fab-d studies. For example, Fab-d failed to bind either the DP178 peptide or the fusion protein M41Δ178, but its epitope was reconstituted by simply mixing these two reagents together (FIG. 10). Again, the proline mutation in the leucine zipper domain of the fusion protein, M41-PA178, failed to reconstitute the epitope in similar mixing experiments.

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9. EXAMPLE: METHOD FOR COMPUTER-ASSISTED
IDENTIFICATION OF DP-107-LIKE
AND DP-178-LIKE SEQUENCES

A number of known coiled-coil sequences have been well described in the literature and contain heptad repeat positioning for each amino acid. Coiled-coil nomenclature labels each of seven amino acids of a heptad repeat A through G, with amino acids A and D tending to be hydrophobic positions. Amino acids E and G tend to be charged. These four positions (A, D, E, and G) form the amphipathic backbone structure of a monomeric alpha-helix. The backbones of two or more amphipathic helices interact with each other to form di-, tri-, tetrameric, etc., coiled-coil structures. In order to begin to design computer search motifs, a series of well characterized coiled coils were chosen including yeast transcription factor GCN4, Influenza Virus hemagglutinin loop 36, and human proto-oncogenes c-Myc, c-Fos, and c-Jun. For each peptide sequence, a strict homology for the A and D positions, and a list of the amino acids which could be excluded for the B, C, E, F, and G positions (because they are not observed in these positions) was determined. Motifs were tailored to the DP-107 and DP-178 sequences by deducing the most likely possibilities for heptad positioning of the amino acids of HIV-1 Bru DP-107, which is known to have coiled-coil structure, and HIV-1 Bru DP-178, which is still structurally undefined. The analysis of each of the sequences is contained in FIG. 12. For example, the motif for GCN4 was designed as follows:

1. The only amino acids (using standard single letter amino acid codes) found in the A or D positions of GCN4 were [LMNV].
2. All amino acids were found at B, C, E, F, and G positions except {CFGIMPTW}.

3. The PESEARCH motif would, therefore, be written as follows:

[LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-
 [LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-
 [LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-
 5 [LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)

Translating or reading the motif: "at the first A position either L, M, N, or V must occur; at positions B and C (the next two positions) accept everything
 10 except C, F, G, I, M, P, T, or W; at the D position either L, M, N, or V must occur; at positions E, F, and G (the next 3 positions) accept everything except C, F, G, I, M, P, T, or W." This statement is
 15 contained four times in a 28-mer motif and five times in a 35-mer motif. The basic motif key then would be: [LMNV]-{CFGIMPTW}. The motif keys for the remaining well described coiled-coil sequences are summarized in FIG. 12.

The motif design for DP-107 and DP-178 was
 20 slightly different than the 28-mer model sequences described above due to the fact that heptad repeat positions are not defined and the peptides are both longer than 28 residues. FIG. 13 illustrates several possible sequence alignments for both DP-107 and DP-
 25 178 and also includes motif designs based on 28^{-mer}, 35^{-mer}, and full-length peptides. Notice that only slight differences occur in the motifs as the peptides are lengthened. Generally, lengthening the base peptide results in a less stringent motif. This is
 30 very useful in broadening the possibilities for identifying DP-107-or DP-178-like primary amino acid sequences referred to in this document as "hits".

In addition to making highly specific motifs for each type peptide sequence to be searched, it is also
 35 possible to make "hybrid" motifs. These motifs are

made by "crossing" two or more very stringent motifs to make a new search algorithm which will find not only both "parent" motif sequences but also any peptide sequences which have similarities to one, the other, or both "parents". For example, in Table 3 the "parent" sequence of GCN4 is crossed with each of the possible "parent" motifs of DP-107. Now the hybrid motif must contain all of the amino acids found in the A and D positions of both parents, and exclude all of the amino acids not found in either parent at the other positions. The resulting hybrid from crossing GCN4 or [LMNV]{CFGIMPTW} and DP-107 (28-mer with the first L in the D position) or [ILQT]{CDFIMPST}, is [ILMNQTV]{CFIMPT}. Notice that now only two basic hybrid motifs exist which cover both framing possibilities, as well as all peptide lengths of the parent DP-107 molecule. FIG. 15 represents the hybridizations of GCN4 with DP-178. FIG. 16 represents the hybridizations of DP-107 and DP-178. It is important to keep in mind that the represented motifs, both parent and hybrid, are motif keys and not the depiction of the full-length motif needed to actually do the computer search.

Hybridizations can be performed on any combination of two or more motifs. Table 5 summarizes several three-motif hybridizations including GCN4, DP-107 (both frames), and DP-178 (also both frames). Notice that the resulting motifs are now becoming much more similar to each other. In fact, the first and third hybrid motifs are actually subsets of the second and fourth hybrid motifs respectively. This means that the first and third hybrid motifs are slightly more stringent than the second and fourth. It should also be noted that with only minor changes in these four motifs, or by hybridizing them, a single motif could be obtained

which would find all of the sequences. However, it should be remembered that stringency is also reduced. Finally, the most broad-spectra and least-stringent hybrid motif is described in FIG. 18 which summarizes the hybridization of GCN4, DP-107 (both frames), DP-178 (both frames), c-Fos, c-Jun, c-Myc, and Flu loop 36.

A special set of motifs was designed based on the fact that DP-178 is located only approximately ten amino acids upstream of the transmembrane spanning region of gp41 and just C-terminal to a proline which separates DP-107 and DP-178. It has postulated that DP-178 may be an amphipathic helix when membrane associated, and that the proline might aid in the initiation of the helix formation. The same arrangement was observed in Respiratory Syncytial Virus; however, the DP-178-like region in this virus also had a leucine zipper just C-terminal to the proline. Therefore, designed N-terminal proline-leucine zipper motifs were designed to analyze whether any other viruses might contain this same pattern. The motifs are summarized in FIG. 19.

The PC/Gene protein database contains 5879 viral amino acid sequences (library file PVIRUSES; CD-ROM release 11.0). Of these, 1092 are viral envelope or glycoprotein sequences (library file PVIRUSE1). Tables V through X contain lists of protein sequence names and motif hit locations for all the motifs searched.

10. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION
OF DP-107 AND DP-178-LIKE SEQUENCES
IN HUMAN IMMUNODEFICIENCY VIRUS

FIG. 20 represents search results for HIV-1 BRU isolate gp41 (PC/Gene protein sequence PENV_HV1BR). Notice that the hybrid motif which crosses DP-107 and

DP-178 (named 107x178x4; the same motif as found in FIG. 16 found three hits including amino acids 550-599, 636-688, and 796-823. These areas include DP-107 plus eight N-terminal and four C-terminal amino acids; DP-178 plus seven N-terminal and ten C-terminal amino acids; and an area inside the transmembrane region (cytoplasmic). FIG. 20 also contains the results obtained from searching with the motif named ALLMOTI5, for which the key is found in FIG. 17 ({CDGHP}{CFP}x5). This motif also found three hits including DP-107 (amino acids 510-599), DP-178 (615-717), and a cytoplasmic region (772-841). These hits overlap the hits found by the motif 107x178x4 with considerable additional sequences on both the amino and carboxy termini. This is not surprising in that 107x178x4 is a subset of the ALLMOTI5 hybrid motif. Importantly, even though the stringency of ALLMOTI5 is considerably less than 107x178x4, it still selectively identifies the DP-107 and DP-178 regions of gp41 shown to contain sequences for inhibitory peptides of HIV-1. The results of these two motif searches are summarized in Table V under the PC/Gene protein sequence name PENV HV1BR. The proline-leucine zipper motifs also gave several hits in HIV-1 BRU including 503-525 which is at the very C-terminus of gp120, just upstream of the cleavage site (P7LZIPC and P12LZIPC); and 735-768 in the cytoplasmic domain of gp41 (P23LZIPC). These results are found in Tables VIII, IX, and X under the same sequence name as mentioned above. Notice that the only area of HIV-1 BRU which is predicted by the Lupas algorithm to contain a coiled-coil region, is from amino acids 635-670. This begins eight amino acids N-terminal to the start and ends eight amino acids N-terminal to the end of DP-178. DP-107, despite the fact that it is a known coiled coil, is

not predicted to contain a coiled-coil region using the Lupas method.

11. **EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP-107-LIKE AND DP-178-LIKE SEQUENCES IN HUMAN RESPIRATORY SYNCYTIAL VIRUS**

FIG. 21 represents search results for Human Respiratory Syncytial Virus (RSV; Strain A2) fusion glycoprotein F1 (PC/Gene protein sequence name PVGLF_HRSVA). Motif 107x178x4 finds three hits including amino acids 152-202, 213-243, and 488-515. The arrangement of these hits is similar to what is found in HIV-1 except that the motif finds two regions with similarities to DP-178, one just downstream of what would be called the DP-107 region or amino acids 213-243, and one just upstream of the transmembrane region (also similar to DP-178) or amino acids 488-515. Motif ALLMOTI5 also finds three areas including amino acids 116-202, 267-302, and 506-549. The proline-leucine zipper motifs also gave several hits including amino acids 205-221 and 265-287 (P1LZIPC 265-280, P12LZIPC), and 484-513 (P7LZIPC and P12LZIPC 484-506, P23LZIPC). Notice that the PLZIP motifs also identify regions which share location similarities with DP-178 of HIV-1.

12. **EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP-107-LIKE AND DP-178-LIKE SEQUENCES IN SIMIAN IMMUNODEFICIENCY VIRUS**

Motif hits for Simian immunodeficiency Virus gp41 (AGM3 isolate; PC/Gene protein sequence name PENV_SIVAG) are shown in FIG. 22. Motif 107x178x4 finds three hits including amino acids 566-593, 597-624, and 703-730. The first two hits only have three amino acids between them and could probably be combined into one hit from 566-624 which would

represent a DP-107-like hit. Amino acids 703 to 730 would then represent a DP-178-like hit. ALLMOTI5 also finds three hits including amino acids 556-628 (DP-107-like), 651-699 (DP-178-like), and 808-852 which represents the transmembrane spanning region. SIV
5 also has one region from 655-692 with a high propensity to form a coiled coil as predicted by the Lupas algorithm. Both 107x178x4 and ALLMOTI5 motifs find the same region. SIV does not have any PLZIP motif hits in gp41.

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13. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP-107-LIKE AND DP-178 LIKE SEQUENCES
IN CANINE DISTEMPER VIRUS

Canine Distemper Virus (strain Onderstepoort)

15 fusion glycoprotein F1 (PC/Gene Protein sequence name PVGLF_CDVO) has regions similar to Human RSV which are predicted to be DP-107-like and DP-178-like (FIG. 23). Motif 107x178x4 highlights one area just C-terminal to the fusion peptide at amino acids 252-293. Amino
20 acids 252-286 are also predicted to be coiled coil using the Lupas algorithm. Almost 100 amino acids C-terminal to the first region is a DP-178-like area at residues 340-367. ALLMOTI5 highlights three areas of interest including: amino acids 228-297, which
25 completely overlaps both the Lupas prediction and the DP-107-like 107x178x4 hit; residues 340-381, which overlaps the second 107x178x4 hit; and amino acids 568-602, which is DP178-like in that it is located just N-terminal to the transmembrane region. It also
30 overlaps another region (residues 570-602) predicted by the Lupas method to have a high propensity to form a coiled coil. Several PLZIP motifs successfully identified areas of interest including P6 and P12LZIPC which highlight residues 336-357 and 336-361
35 respectively; P1 and P12LZIPC which find residues 398-

414; and P12 and P23LZIPC which find residues 562-589 and 562-592 respectively.

14. **EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP-107-LIKE AND DP-178-LIKE SEQUENCES
IN NEWCASTLE DISEASE VIRUS**

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FIG. 24 shows the motif hits found in Newcastle Disease Virus (strain Australia-Victoria/32; PC Gene protein sequence name PVGLF_NDVA). Motif 107x178x4 finds two areas including a DP-107-like hit at amino acids 151-178 and a DP-178-like hit at residues 426-512. ALLMOTI5 finds three areas including residues 117-182, 231-272, and 426-512. The hits from 426-512 include a region which is predicted by the Lupas method to have a high coiled-coil propensity (460-503). The PLZIP motifs identify only one region of interest at amino acids 273-289 (P1 and 12LZIPC).

15. **EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION
OF DP-107-LIKE AND DP-178-LIKE
SEQUENCES IN HUMAN PARAINFLUENZA VIRUS**

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Both motifs 107x178x4 and ALLMOTI5 exhibit DP-107-like hits in the same region, 115-182 and 117-182 respectively, of Human Parainfluenza Virus (strain NIH 47885; PC/Gene protein sequence name PVGLF_p13H4; (FIG. 25). In addition, the two motifs have a DP-178-like hit just slightly C-terminal at amino acids 207-241. Both motifs also have DP-178-like hits nearer the transmembrane region including amino acids 457-497 and 462-512 respectively. Several PLZIP motif hits are also observed including 283-303 (P5LZIPC), 283-310 (P12LZIPC), 453-474 (P6LZIPC), and 453-481 (P23LZIPC). The Lupas algorithm predicts that amino acids 122-176 have a propensity to form a coiled-coil.

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16. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP-107-LIKE AND DP-178-LIKE SEQUENCES OF
INFLUENZA A VIRUS

FIG. 26 illustrates the Lupas prediction for a coiled coil in Influenza A Virus (strain A/Aichi/2/68) at residues 379-436, as well as the motif hits for 107x178x4 at amino acids 387-453, and for ALLMOTI5 at residues 380-456. Residues 383-471 (38-125 of HA2) were shown by Carr and Kim to be an extended coiled coil when under acidic pH (Carr and Kim, 1993, Cell 73: 823-832). The Lupas algorithm predicts a coiled-coil at residues 379-436. All three methods successfully predicted the region shown to actually have coiled-coil structure; however, ALLMOTI5 predicted the greatest portion of the 88 residue stretch.

17. EXAMPLE: RSV ANTIVIRAL COMPOUNDS

In the Example presented herein, respiratory syncytial virus (RSV) peptide sequences identified by utilizing the computer-assisted coiled-coil peptide sequence searches described in Example 9, above, are shown to encode peptide domains that exhibit structural similarity to actual, known coiled-coil peptides, and are, additionally found to exhibit antiviral activity.

17.1 MATERIALS AND METHODS

Structural analyses consisted of circular dichroism (CD) studies, which were conducted according to the methods described in the Applicants' co-pending U.S. Patent Application Ser. No 08/073,028.

Anti-RSV antiviral activity was assayed as described in Pringle, C.R. et al., 1985, J. Medical Vir. 17:377-386.

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A 48 amino acid RSV F2 peptide and a 53 amino acid RSV T67 peptide are utilized which span sequences that were identified via the computer assisted peptide sequence search strategies described in Example 9, above. See FIG. 21 for the exact position of these sequences and for the motifs utilized.

17.2 RESULTS

35-mer oligopeptides were synthesized which constituted portions of the 48 amino acid RSV F2 peptide sequence (FIG. 27) and portions of the 53 amino acid RSV T67 peptide sequence (FIG. 28). The oligopeptides were assayed, via CD analysis, for structural similarity to known coiled-coil structures, and for anti-RSV activity. As shown in FIGS. 27 and 28, a number of these oligopeptides exhibited substantial coiled-coil structural similarity and/or antiviral activity.

Thus, the computer assisted searches described, herein, in Example 9, for example, successfully identified viral peptide domains that represent highly promising anti-RSV antiviral compounds.

18. EXAMPLE: HPF3 ANTIVIRAL COMPOUNDS

In the Example presented herein, human parainfluenza virus 3 (HPF3) peptide sequences identified by utilizing the computer-assisted coiled-coil peptide sequence searches described in Example 9, above, are shown to encode peptide domains that exhibit structural similarity to actual, known coiled-coil peptides, and are, additionally found to exhibit antiviral activity.

18.1 MATERIALS AND METHODS

Structural analyses consisted of circular dichroism (CD) studies, which were conducted according

to the methods described in the Applicants' co-pending U.S. Patent Application Ser. No 08/073,028.

Anti-HPF3 antiviral activity was assayed as described in Pringle, C.R. et al., 1985, J. Medical Vir. 17:377-386.

5 A 56 amino acid and 70 amino acid HPF3 peptide are utilized which span sequences that were identified via the computer assisted peptide sequence search strategies described in Example 9, above. See FIG. 25 for the exact positions of these sequences and for the
10 motifs utilized.

18.2 RESULTS

35-mer oligopeptides were synthesized which constituted portions of the 56 amino acid HPF3 peptide
15 sequence (FIG. 29) and portions of the 70 amino acid HPF3 peptide sequence (FIG. 30). The oligopeptides were assayed, via CD analysis, for structural similarity to known coiled-coil structures, and for anti-HPF3 activity. As shown in FIGS. 29 and 30, a
20 number of these oligopeptides exhibited substantial coiled-coil structural similarity and/or antiviral activity.

Thus, the computer assisted searches described, herein, in Example 9, for example, successfully
25 identified viral peptide domains that represent highly promising anti-HPF3 antiviral compounds.

The present invention is not to be limited in scope by the specific embodiments described which are
30 intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will
35 become apparent to those skilled in the art from the

foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. A peptide having an amino acid sequence corresponding to an α -helix region of an extracellular domain of a viral envelope protein, which interacts
5 with and binds to a second α -helix region of the viral envelope protein containing a leucine-zipper domain having a coiled-coil structure.

2. The peptide of Claim 1 wherein the peptide
10 is recognized by a computer-assisted peptide sequence search utilizing an ALLMOTI5, 107x178x4 motif, or a PLZIP motif.

3. The peptide of Claim 1 in which the
15 enveloped virus is a retrovirus.

4. The peptide of Claim 3 in which the retrovirus is a human retrovirus.

20 5. The peptide of Claim 4 in which the human retrovirus is HIV-1 or HIV-2.

6. The peptide of Claim 4 in which the human
25 retrovirus is HTLV-I or HTLV-II

7. The peptide of Claim 1 in which the enveloped virus is a non-human retrovirus.

8. The peptide of Claim 6 in which the non-
30 human retrovirus is bovine leukosis virus, feline sarcoma virus, feline leukemia virus, simian immunodeficiency virus, simian sarcoma virus, and sheep progress pneumonia virus.

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9. The peptide of Claim 1 in which the enveloped virus is a non-retroviral virus.

10. The peptide of Claim 9 in which the virus is respiratory syncytial virus, influenza virus,
 5 parainfluenza virus, canine distemper virus, or newcastle disease virus.

11. A peptide having a formula selected from the group consisting of:

10 X-YTS-Z
 X-YTSL-Z
 X-YTSLI-Z
 X-YTSLIH-Z
 X-YTSLIHS-Z
 X-YTSLIHSL-Z
 X-YTSLIHSLI-Z
 15 X-YTSLIHSLIE-Z
 X-YTSLIHSLIEE-Z
 X-YTSLIHSLIEES-Z
 X-YTSLIHSLIEESQ-Z
 X-YTSLIHSLIEESQN-Z
 X-YTSLIHSLIEESQNNQ-Z
 X-YTSLIHSLIEESQNNQQ-Z
 X-YTSLIHSLIEESQNNQQE-Z
 20 X-YTSLIHSLIEESQNNQQEK-Z
 X-YTSLIHSLIEESQNNQQEKN-Z
 X-YTSLIHSLIEESQNNQQEKNE-Z
 X-YTSLIHSLIEESQNNQQEKNEQ-Z
 X-YTSLIHSLIEESQNNQQEKNEQE-Z
 X-YTSLIHSLIEESQNNQQEKNEQEL-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLE-Z
 25 X-YTSLIHSLIEESQNNQQEKNEQELLEL-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELD-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDK-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKW-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWA-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASL-Z
 30 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLW-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWN-Z
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWNW-Z and
 X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID:1), or

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5 X-NWF-Z
 X-WNWF-Z
 X-LWNWF-Z
 X-SLWNWF-Z
 X-ASLWNWF-Z
 X-WASLWNWF-Z
 X-KWASLWNWF-Z
 X-DKWASLWNWF-Z
 X-LDKWASLWNWF-Z
 X-ELDKWASLWNWF-Z
 X-LELDKWASLWNWF-Z
 X-LLELDKWASLWNWF-Z
 X-ELLELDKWASLWNWF-Z
 X-QELLELDKWASLWNWF-Z
 X-EQELLELDKWASLWNWF-Z
 10 X-NEQELLELDKWASLWNWF-Z
 X-KNEQELLELDKWASLWNWF-Z
 X-EKNEQELLELDKWASLWNWF-Z
 X-QEKNEQELLELDKWASLWNWF-Z
 X-QQEKNEQELLELDKWASLWNWF-Z
 X-NQEKNEQELLELDKWASLWNWF-Z
 X-QNQEKNEQELLELDKWASLWNWF-Z
 15 X-SQNQEKNEQELLELDKWASLWNWF-Z
 X-ESQNQEKNEQELLELDKWASLWNWF-Z
 X-EESQNQEKNEQELLELDKWASLWNWF-Z
 X-IEESQNQEKNEQELLELDKWASLWNWF-Z
 X-SLIEESQNQEKNEQELLELDKWASLWNWF-Z
 X-HSLIEESQNQEKNEQELLELDKWASLWNWF-Z
 X-IHSLIEESQNQEKNEQELLELDKWASLWNWF-Z
 20 X-LIHSLIEESQNQEKNEQELLELDKWASLWNWF-Z
 X-SLIHSLIEESQNQEKNEQELLELDKWASLWNWF-Z
 and X-TSLIHSLIEESQNQEKNEQELLELDKWASLWNWF-Z

in which:

25 amino acid residues are presented by the single-
 letter code;
 X comprises an amino group, an acetyl group, a 9-
 fluorenylmethoxy-carbonyl group, a
 hydrophobic group, or a macromolecule
 30 carrier group;
 Z comprises a carboxyl group, an amido group, a
 hydrophobic group, or a macromolecular
 carrier group.

35 12. A peptide having a formula selected from the
 group consisting of:

X-LEA-Z
 X-LEAN-Z
 X-LEANI-Z
 X-LEANIS-Z
 X-LEANISQ-Z
 X-LEANISQS-Z
 X-LEANISQSL-Z
 5 X-LEANISQSLE-Z
 X-LEANISQSLEQ-Z
 X-LEANISQSLEQA-Z
 X-LEANISQSLEQAQ-Z
 X-LEANISQSLEQAQI-Z
 X-LEANISQSLEQAQIQ-Z
 X-LEANISQSLEQAQIQQ-Z
 10 X-LEANISQSLEQAQIQQE-Z
 X-LEANISQSLEQAQIQQEK-Z
 X-LEANISQSLEQAQIQQEKN-Z
 X-LEANISQSLEQAQIQQEKNM-Z
 X-LEANISQSLEQAQIQQEKNMY-Z
 X-LEANISQSLEQAQIQQEKNMYE-Z
 X-LEANISQSLEQAQIQQEKNMYEL-Z
 X-LEANISQSLEQAQIQQEKNMYELQ-Z
 15 X-LEANISQSLEQAQIQQEKNMYELQK-Z
 X-LEANISQSLEQAQIQQEKNMYELQKL-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLN-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNS-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSW-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWD-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDV-Z
 20 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFT-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTN-Z
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNW-Z and
 X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z (SEQ ID:7), or

X-NWL-Z
 X-TNWL-Z
 25 X-FTNWL-Z
 X-VFTNWL-Z
 X-DVFTNWL-Z
 X-WDVFTNWL-Z
 X-SWDVFTNWL-Z
 X-NSWDVFTNWL-Z
 X-LNSWDVFTNWL-Z
 30 X-KLNSWDVFTNWL-Z
 X-QKLNSWDVFTNWL-Z
 X-LQKLNSWDVFTNWL-Z
 X-ELQKLNSWDVFTNWL-Z
 X-YELQKLNSWDVFTNWL-Z
 X-MYELQKLNSWDVFTNWL-Z
 X-NMYELQKLNSWDVFTNWL-Z
 X-KNMYELQKLNSWDVFTNWL-Z
 35 X-EKNMYELQKLNSWDVFTNWL-Z
 X-QEKNMYELQKLNSWDVFTNWL-Z

X-QQEKMYELQKLNSWDVFTNWL-Z
 X-IQQEKMYELQKLNSWDVFTNWL-Z
 X-QIQQEKMYELQKLNSWDVFTNWL-Z
 X-AQIQQEKMYELQKLNSWDVFTNWL-Z
 X-QAQIQQEKMYELQKLNSWDVFTNWL-Z
 X-EAQIQQEKMYELQKLNSWDVFTNWL-Z
 X-LEAQIQQEKMYELQKLNSWDVFTNWL-Z
 X-SLEAQIQQEKMYELQKLNSWDVFTNWL-Z
 X-QKSLEAQIQQEKMYELQKLNSWDVFTNWL-Z
 X-SQSLEAQIQQEKMYELQKLNSWDVFTNWL-Z
 X-ISQSLEAQIQQEKMYELQKLNSWDVFTNWL-Z
 X-NISQSLEAQIQQEKMYELQKLNSWDVFTNWL-Z
 X-ANISQSLEAQIQQEKMYELQKLNSWDVFTNWL-Z
 and X-EANISQSLEAQIQQEKMYELQKLNSWDVFTNWL-Z

5

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in which:

amino acid residues are presented by the single-letter code;

15

X comprises an amino group, an acetyl group, a 9-fluoromethoxymethyl-carbonyl group, a hydrophobic group, or a macromolecule carrier group;

20

Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

13. A peptide having a formula selected from the group consisting of:

X-YTS-Z
 X-YTSV-Z
 25 X-YTSVI-Z
 X-YTSVIT-Z
 X-YTSVITI-Z
 X-YTSVITIE-Z
 X-YTSVITIEL-Z
 X-YTSVITIELS-Z
 X-YTSVITIELSN-Z
 30 X-YTSVITIELSNI-Z
 X-YTSVITIELSNIK-Z
 X-YTSVITIELSNIKE-Z
 X-YTSVITIELSNIKEN-Z
 X-YTSVITIELSNIKENK-Z
 X-YTSVITIELSNIKENKC-Z
 X-YTSVITIELSNIKENKCN-Z
 X-YTSVITIELSNIKENKCNG-Z
 35 X-YTSVITIELSNIKENKCNGT-Z
 X-YTSVITIELSNIKENKCNGTD-Z

X-YTSVITIELSNIKENKCNGTDA-Z
 X-YTSVITIELSNIKENKCNGTDAK-Z
 X-YTSVITIELSNIKENKCNGTDAKV-Z
 X-YTSVITIELSNIKENKCNGTDAKVK-Z
 X-YTSVITIELSNIKENKCNGTDAKVKL-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLI-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIK-Z
 5 X-YTSVITIELSNIKENKCNGTDAKVKLIQ-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQE-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQEL-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELD-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDK-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKY-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYK-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKN-Z
 10 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNA-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAV-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTE-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTEL-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQ-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQLL-Z
 15 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQLLM-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQLLMQ-Z
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQLLMQS-Z and
 X-YTSVITIELSNIKENKCNGTDAKVKLIQELDKYKNAVTELQLLMQST-Z, or

 X-QST-Z
 X-MQST-Z
 20 X-LMQST-Z
 X-LLMQST-Z
 X-QLLMQST-Z
 X-LQLLMQST-Z
 X-ELQLLMQST-Z
 X-TELQLLMQST-Z
 X-VTELQLLMQST-Z
 X-AVTELQLLMQST-Z
 25 X-NAVTELQLLMQST-Z
 X-KNAVTELQLLMQST-Z
 X-YKNAVTELQLLMQST-Z
 X-KYKNAVTELQLLMQST-Z
 X-DKYKNAVTELQLLMQST-Z
 X-LDKYKNAVTELQLLMQST-Z
 X-ELDKYKNAVTELQLLMQST-Z
 30 X-QELDKYKNAVTELQLLMQST-Z
 X-KQELDKYKNAVTELQLLMQST-Z
 X-IKQELDKYKNAVTELQLLMQST-Z
 X-LIKQELDKYKNAVTELQLLMQST-Z
 X-KLIKQELDKYKNAVTELQLLMQST-Z
 X-VKLIKQELDKYKNAVTELQLLMQST-Z
 X-KVKLIKQELDKYKNAVTELQLLMQST-Z
 35 X-AKVLIKQELDKYKNAVTELQLLMQST-Z
 X-DAKVLIKQELDKYKNAVTELQLLMQST-Z

X-TDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-GTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-NGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-CNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-KCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-NKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-ENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 5 X-KENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-IKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-NIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-SNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-LSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-ELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-IELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 10 X-TIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-ITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-VITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-SVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z
 X-TSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-Z

in which:

15 amino acid residues are presented by the single-
 letter code;
 X comprises an amino group, an acetyl group, a 9-
 fluoromethoxymethyl-carbonyl group, a
 hydrophobic group, or a macromolecule
 carrier group;
 20 Z comprises a carboxyl group, an amido group, a
 hydrophobic group, or a macromolecular
 carrier group.

25 14. A peptide having a formula selected from the
 group consisting of:

X-FYD-Z
 X-FYDP-Z
 X-FYDPL-Z
 X-FYDPLV-Z
 X-FYDPLVF-Z
 30 X-FYDPLVFP-Z
 X-FYDPLVFPS-Z
 X-FYDPLVFPSD-Z
 X-FYDPLVFPSDE-Z
 X-FYDPLVFPSDEF-Z
 X-FYDPLVFPSDEFD-Z
 X-FYDPLVFPSDEFDA-Z
 35 X-FYDPLVFPSDEFDAS-Z
 X-FYDPLVFPSDEFDASI-Z

X-FYDPLVFPSEFDASIS-Z
 X-FYDPLVFPSEFDASISQ-Z
 X-FYDPLVFPSEFDASISQV-Z
 X-FYDPLVFPSEFDASISQVN-Z
 X-FYDPLVFPSEFDASISQVNE-Z
 X-FYDPLVFPSEFDASISQVNEK-Z
 X-FYDPLVFPSEFDASISQVNEKI-Z
 5 X-FYDPLVFPSEFDASISQVNEKIN-Z
 X-FYDPLVFPSEFDASISQVNEKINQ-Z
 X-FYDPLVFPSEFDASISQVNEKINQS-Z
 X-FYDPLVFPSEFDASISQVNEKINQSL-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLA-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLAF-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLAFI-Z
 10 X-FYDPLVFPSEFDASISQVNEKINQSLAFIR-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLAFIRK-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLAFIRKS-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLAFIRKSD-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLAFIRKSDE-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLAFIRKSDEL-Z
 X-FYDPLVFPSEFDASISQVNEKINQSLAFIRKSDELL-Z, or

 15 X-DELL-Z
 X-SDELL-Z
 X-KSDELL-Z
 X-RKSDELL-Z
 X-IRKSDELL-Z
 X-FIRKSDELL-Z
 X-AFIRKSDELL-Z
 X-LAFIRKSDELL-Z
 20 X-SLAFIRKSDELL-Z
 X-QSLAFIRKSDELL-Z
 X-NQSLAFIRKSDELL-Z
 X-INQSLAFIRKSDELL-Z
 X-KINQSLAFIRKSDELL-Z
 X-EKINQSLAFIRKSDELL-Z
 X-NEKINQSLAFIRKSDELL-Z
 25 X-VNEKINQSLAFIRKSDELL-Z
 X-QVNEKINQSLAFIRKSDELL-Z
 X-SQVNEKINQSLAFIRKSDELL-Z
 X-ISQVNEKINQSLAFIRKSDELL-Z
 X-SISQVNEKINQSLAFIRKSDELL-Z
 X-ASISQVNEKINQSLAFIRKSDELL-Z
 X-DASISQVNEKINQSLAFIRKSDELL-Z
 X-FDASISQVNEKINQSLAFIRKSDELL-Z
 30 X-EFDASISQVNEKINQSLAFIRKSDELL-Z
 X-DEFDASISQVNEKINQSLAFIRKSDELL-Z
 X-SDEFDASISQVNEKINQSLAFIRKSDELL-Z
 X-PSDEFDASISQVNEKINQSLAFIRKSDELL-Z
 X-FPSDEFDASISQVNEKINQSLAFIRKSDELL-Z
 X-VFPSDEFDASISQVNEKINQSLAFIRKSDELL-Z
 X-LVFPSEFDASISQVNEKINQSLAFIRKSDELL-Z
 35 X-PLVFPSEFDASISQVNEKINQSLAFIRKSDELL-Z
 X-DPLVFPSEFDASISQVNEKINQSLAFIRKSDELL-Z

X-YDPLVFPSEFDASISQVNEKINQSLAFIRKSDELL-Z

in which:

amino acid residues are presented by the single-letter code;

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X comprises an amino group, an acetyl group, a 9-fluoromethoxymethyl-carbonyl group, a hydrophobic group, or a macromolecule carrier group;

10

Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

15 15. A peptide having a formula selected from the group consisting of:

X-ITL-Z
 X-ITLN-Z
 X-ITLNN-Z
 X-ITLNNS-Z
 X-ITLNNSV-Z
 X-ITLNNSVA-Z
 20 X-ITLNNSVAL-Z
 X-ITLNNSVALD-Z
 X-ITLNNSVALDP-Z
 X-ITLNNSVALDPI-Z
 X-ITLNNSVALDPID-Z
 X-ITLNNSVALDPIDI-Z
 X-ITLNNSVALDPIDIS-Z
 X-ITLNNSVALDPIDISI-Z
 25 X-ITLNNSVALDPIDISIE-Z
 X-ITLNNSVALDPIDISIEL-Z
 X-ITLNNSVALDPIDISIELN-Z
 X-ITLNNSVALDPIDISIELNK-Z
 X-ITLNNSVALDPIDISIELNKA-Z
 X-ITLNNSVALDPIDISIELNKAK-Z
 X-ITLNNSVALDPIDISIELNKAKS-Z
 X-ITLNNSVALDPIDISIELNKAKSD-Z
 30 X-ITLNNSVALDPIDISIELNKAKSDL-Z
 X-ITLNNSVALDPIDISIELNKAKSDLE-Z
 X-ITLNNSVALDPIDISIELNKAKSDLEE-Z
 X-ITLNNSVALDPIDISIELNKAKSDLEES-Z
 X-ITLNNSVALDPIDISIELNKAKSDLEESK-Z
 X-ITLNNSVALDPIDISIELNKAKSDLEESKE-Z
 X-ITLNNSVALDPIDISIELNKAKSDLEESKEW-Z
 35 X-ITLNNSVALDPIDISIELNKAKSDLEESKEWI-Z
 X-ITLNNSVALDPIDISIELNKAKSDLEESKEWIR-Z

X-ITLNNVALDPIDISIELNKAUSDLEESKEWIRR-Z
 X-ITLNNVALDPIDISIELNKAUSDLEESKEWIRRS-Z, or

5 X-RRS-Z
 X-IRRS-Z
 X-WIRRS-Z
 X-EWIRRS-Z
 X-KEWIRRS-Z
 X-SKEWIRRS-Z
 X-ESKEWIRRS-Z
 X-EESKEWIRRS-Z
 X-LEESKEWIRRS-Z
 X-DLEESKEWIRRS-Z
 X-SDLEESKEWIRRS-Z
 10 X-KSDLEESKEWIRRS-Z
 X-AKSDLEESKEWIRRS-Z
 X-KAKSDLEESKEWIRRS-Z
 X-NKAKSDLEESKEWIRRS-Z
 X-LNKAUSDLEESKEWIRRS-Z
 X-ELNKAUSDLEESKEWIRRS-Z
 X-IELNKAUSDLEESKEWIRRS-Z
 X-SIELNKAUSDLEESKEWIRRS-Z
 15 X-ISIELNKAUSDLEESKEWIRRS-Z
 X-DISIELNKAUSDLEESKEWIRRS-Z
 X-IDISIELNKAUSDLEESKEWIRRS-Z
 X-PIDISIELNKAUSDLEESKEWIRRS-Z
 X-DPIDISIELNKAUSDLEESKEWIRRS-Z
 X-LDPIDISIELNKAUSDLEESKEWIRRS-Z
 X-ALDPIDISIELNKAUSDLEESKEWIRRS-Z
 20 X-VALDPIDISIELNKAUSDLEESKEWIRRS-Z
 X-SVALDPIDISIELNKAUSDLEESKEWIRRS-Z
 X-NSVALDPIDISIELNKAUSDLEESKEWIRRS-Z
 X-NNSVALDPIDISIELNKAUSDLEESKEWIRRS-Z
 X-LNNSVALDPIDISIELNKAUSDLEESKEWIRRS-Z
 X-TLNNVALDPIDISIELNKAUSDLEESKEWIRRS-Z

in which:

25 amino acid residues are presented by the single-
 letter code;
 X comprises an amino group, an acetyl group, a 9-
 fluoromethoxymethyl-carbonyl group, a
 hydrophobic group, or a macromolecule
 30 carrier group;
 Z comprises a carboxyl group, an amido group, a
 hydrophobic group, or a macromolecular
 carrier group.

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16. A peptide having a formula selected from the group consisting of:

- X-ALG-Z
 X-ALGV-Z
 X-ALGVA-Z
 X-ALGVAT-Z
 5 X-ALGVATS-Z
 X-ALGVATSA-Z
 X-ALGVATSAQ-Z
 X-ALGVATSAQI-Z
 X-ALGVATSAQIT-Z
 X-ALGVATSAQITA-Z
 X-ALGVATSAQITAA-Z
 10 X-ALGVATSAQITA-AV-Z
 X-ALGVATSAQITA-AVA-Z
 X-ALGVATSAQITA-AVAL-Z
 X-ALGVATSAQITA-AVALV-Z
 X-ALGVATSAQITA-AVALVE-Z
 X-ALGVATSAQITA-AVALVEA-Z
 X-ALGVATSAQITA-AVALVEAK-Z
 X-ALGVATSAQITA-AVALVEAKQ-Z
 15 X-ALGVATSAQITA-AVALVEAKQA-Z
 X-ALGVATSAQITA-AVALVEAKQAR-Z
 X-ALGVATSAQITA-AVALVEAKQARS-Z
 X-ALGVATSAQITA-AVALVEAKQARSD-Z
 X-ALGVATSAQITA-AVALVEAKQARSDI-Z
 X-ALGVATSAQITA-AVALVEAKQARSDIE-Z
 X-ALGVATSAQITA-AVALVEAKQARSDIEK-Z
 20 X-ALGVATSAQITA-AVALVEAKQARSDIEKL-Z
 X-ALGVATSAQITA-AVALVEAKQARSDIEKLK-Z
 X-ALGVATSAQITA-AVALVEAKQARSDIEKLKE-Z
 X-ALGVATSAQITA-AVALVEAKQARSDIEKLKEA-Z
 X-ALGVATSAQITA-AVALVEAKQARSDIEKLKEAI-Z
 X-ALGVATSAQITA-AVALVEAKQARSDIEKLKEAIR-Z
 X-ALGVATSAQITA-AVALVEAKQARSDIEKLKEAIRD-Z, or
 25 X-IRD-Z
 X-AIRD-Z
 X-EAIRD-Z
 X-KEAIRD-Z
 X-LKEAIRD-Z
 X-KLKEAIRD-Z
 X-EKLKEAIRD-Z
 X-IEKLKEAIRD-Z
 30 X-DIEKLKEAIRD-Z
 X-SDIEKLKEAIRD-Z
 X-RSDIEKLKEAIRD-Z
 X-ARSDIEKLKEAIRD-Z
 X-QARSDIEKLKEAIRD-Z
 X-KQARSDIEKLKEAIRD-Z
 X-AKQARSDIEKLKEAIRD-Z
 35 X-EAKQARSDIEKLKEAIRD-Z
 X-VEAKQARSDIEKLKEAIRD-Z

X-LVEAKQARSDIEKLKEAIRD-Z
 X-ALVEAKQARSDIEKLKEAIRD-Z
 X-VALVEAKQARSDIEKLKEAIRD-Z
 X-AVALVEAKQARSDIEKLKEAIRD-Z
 X-AAVALVEAKQARSDIEKLKEAIRD-Z
 X-TAAVALVEAKQARSDIEKLKEAIRD-Z
 X-ITAAVALVEAKQARSDIEKLKEAIRD-Z
 5 X-QITAVALVEAKQARSDIEKLKEAIRD-Z
 X-AQITAVALVEAKQARSDIEKLKEAIRD-Z
 X-SAQITAVALVEAKQARSDIEKLKEAIRD-Z
 X-TSAQITAVALVEAKQARSDIEKLKEAIRD-Z
 X-ATSAQITAVALVEAKQARSDIEKLKEAIRD-Z
 X-VATSAQITAVALVEAKQARSDIEKLKEAIRD-Z
 X-GVATSAQITAVALVEAKQARSDIEKLKEAIRD-Z
 10 X-LGVATSAQITAVALVEAKQARSDIEKLKEAIRD-Z

in which:

amino acid residues are presented by the single-letter code;

X comprises an amino group, an acetyl group, a 9-fluoromethoxymethyl-carbonyl group, a hydrophobic group, or a macromolecule carrier group;

Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

17. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein X is a hydrophobic group.

18. The peptide of Claim 17 wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

19. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein Z is a hydrophobic group.

20. The peptide of Claim 19 wherein the hydrophobic group Z is t-butyloxycarbonyl.

35

21. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein X is a macromolecular carrier group.

22. The peptide of Claim 21 wherein the macromolecular carrier group is a lipid-fatty acid conjugate, a polyethylene glycol, or a carbohydrate moiety.

23. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein Z is a macromolecular carrier group.

24. The peptide of Claim 23 wherein the macromolecular carrier group Z is a lipid-fatty acid conjugate, a polyethylene glycol, or a carbohydrate moiety.

25. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein at least one bond linking adjacent amino acid residues is a non-peptide bond.

26. The peptide of Claim 25 wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

27. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein at least one amino acid residue is in a D-isomer configuration.

28. The peptide of Claim 11, 12, 13, 14, 15 or 16 further comprising at least one amino acid insertion.

29. The peptide of Claim 11, 12, 13, 14, 15 or 16 wherein the amino acid insertion is between 1 and 15 amino acid residues.

30. The peptide of Claim 11, 12, 13, 14, 15 or 16 having at least one less amino acid residue, wherein the amino acid residue(s) represents an amino acid deletion, and wherein the peptide comprises at least three amino acid residues.

5

31. The peptide of Claim 11, 12, 13, 14, 15 or 16 further comprising at least one amino acid substitution wherein a first amino acid residue is substituted for a second, different amino acid residue.

10

32. The peptide of Claim 31 wherein the amino acid substitution is a conserved substitution.

15

33. The peptide of Claim 31 wherein the amino acid substitution is a non-conserved substitution.

20

34. A method for the inhibition of transmission of an enveloped virus to a cell, comprising contacting the cell with an effective concentration of the peptide of Claim 1 for an effective period of time so that no infection of the cell by the virus occurs.

25

35. A method for neutralizing an enveloped virus in a host, comprising administering to the host an effective concentration of the peptide of Claim 1 so that the host raises an immune response sufficient to neutralize the virus, and viral infection of uninfected cells in the host is inhibited.

30

36. A method for neutralizing an enveloped virus in a host, comprising administering to the host an effective concentration of an antibody raised against the peptide of Claim 1 so that viral infection of uninfected cells in the host is inhibited.

35

37. A method for the detection of an enveloped virus comprising:

contacting a viral isolate with an effective concentration of the peptide of Claim 1 for an effective amount of time so that viral infectivity is inhibited; and

assaying the viral isolate for viral enzyme activity.

38. A method for the inhibition of transmission of an HIV retrovirus to a cell, comprising contacting the cell with an effective concentration of the peptide of Claim 11 or 12 for an effective period of time so that no infection of the cell by the retrovirus occurs.

39. A method for neutralizing an HIV retrovirus in a host, comprising administering to the host an effective concentration of the peptide of Claim 11 or 12 so that the host raises an immune response sufficient to neutralize the HIV retrovirus, and HIV infection of uninfected cells in the host is inhibited.

40. A method for neutralizing an HIV retrovirus in a host, comprising administering to the host an effective concentration of an antibody raised against the peptide of Claim 11 or 12 so that HIV infection of uninfected cells in the host is inhibited.

41. A method for the detection of HIV, comprising:

contacting a viral isolate with an effective concentration of the peptide of Claim 11 or 12 for an effective amount of time so that HIV viral infectivity is inhibited; and

assaying the viral isolat for retroviral enzyme activity.

42. A method for the inhibition of transmission of a respiratory syncytial virus to a cell, comprising
5 contacting the cell with an effective concentration of the peptide of Claim 13 or 14 for an effective period of time so that no infection of the cell by the virus occurs.

10 43. A method for neutralizing a respiratory syncytial virus in a host, comprising administering to the host an effective concentration of the peptide of Claim 13 or 14 so that the host raises an immune
15 response sufficient to neutralize the virus, and respiratory syncytial virus infection of uninfected cells in the host is inhibited.

44. A method for neutralizing a respiratory syncytial virus in a host comprising administering to
20 the host an effective concentration of an antibody raised against the peptide of Claim 13 or 14 so that respiratory syncytial virus infection of uninfected cells in the host is inhibited.

25 45. A method for the detection of respiratory syncytial virus comprising:
contacting a viral isolate with an effective concentration of the peptide of Claim 13 or 14 for an effective amount of time so that respiratory syncytial
30 viral infectivity is inhibited; and
assaying the viral isolate for respiratory syncytial virus enzyme activity.

46. A method for the inhibition of transmission
35 of a parainfluenza virus to a cell comprising,

contacting the cell with an effective concentration of the peptide of Claim 15 or 16 for an effective period of time so that no infection of the cell by the virus occurs.

5 47. A method for neutralizing a parainfluenza virus in a host, comprising administering to the host an effective concentration of the peptide of Claim 15 or 16 so that the host raises an immune response
10 sufficient to neutralize the virus, and parainfluenza infection of uninfected cells in the host is inhibited.

 48. A method for neutralizing a parainfluenza virus in a host comprising administering to the host
15 an effective concentration of an antibody raised against the peptide of Claim 15 or 16 so that parainfluenza infection of uninfected cells in the host is inhibited.

20 49. A method for the detection of parainfluenza virus comprising:
 contacting a viral isolate with an effective concentration of the peptide of Claim 15 or 16 for an effective amount of time so that parainfluenza viral
25 infectivity is inhibited; and
 assaying the viral isolate for parainfluenza virus enzyme activity.

30

35

HIV1LAI (DP-178; SEQ ID:1)	YTSLIHSLIEESNQEQEKNEQELLELDKWASLWNWF
HIV1SF2 (DP-185; SEQ ID:3)	YTNTIYNLLEESNQEQEKNEQELLELDKWASLWNWF
HIV1RF (SEQ ID:4)	YTGIIYNLLEESNQEQEKNEQELLELDKWANLWNWF
HIV1MN (SEQ ID:5)	YTSLIYSLLEKSTQEQEKNEQELLELDKWASLWNWF
HIV2ROD (SEQ ID:6)	LEANISKSLEQAQIQQEKNMYELOKLSNDIFGNWF
HIV2NIHZ (SEQ ID:7)	LEANISQSLEQAQIQQEKNMYELOKLSNDVFTNWL
DP180 (SEQ ID:2)	SSSFLLLEQNNMKLQAEQMLEQINEKHYLEDIS
DP118 (SEQ ID:10)	QQLLDVVKRQQEMLRLTVHGTKNLQARVTAIEKYLKDQ
DP125 (SEQ ID:8)	CCGNLLRAIEAQQHLLQLTVHGIKQLQARILAVERYLKDQ
DP116 (SEQ ID:9)	LQARILAVERYLKDQQQ

FIG.1

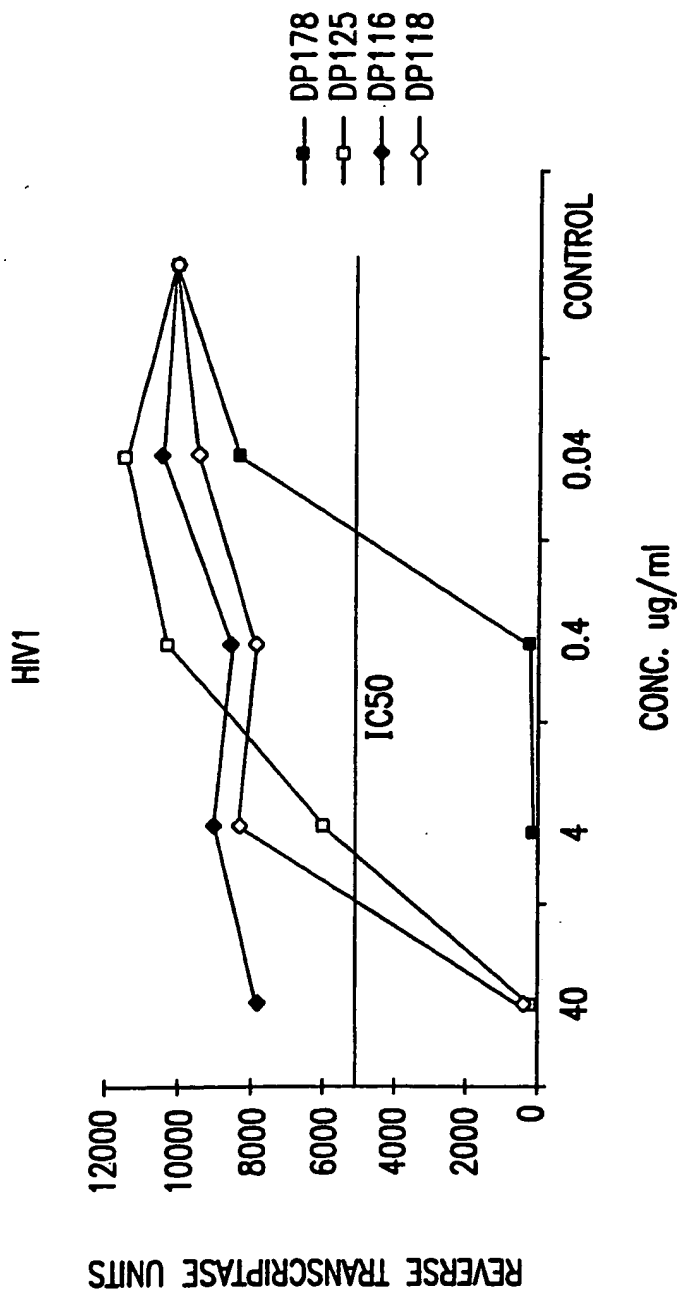


FIG.2

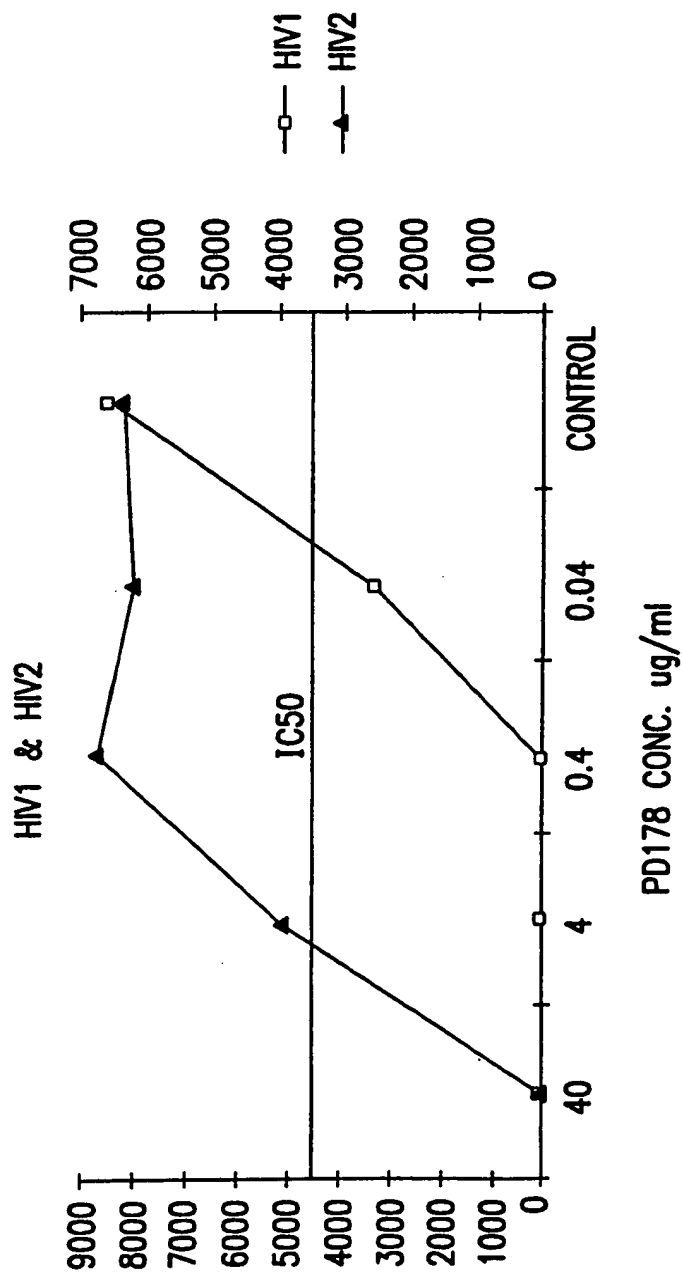


FIG.3

Number of Syncytia/well: concentration in $\mu\text{g/ml}$ (micrograms/ml)									
DP178	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	0	0	0	0	0	0	67
HIV1MN	0	0	0	0	0	ND	ND	ND	34
HIV1RF	0	0	0	0	0	ND	ND	ND	65
HIV1SF2	0	0	0	0	0	ND	ND	ND	58
DP125	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	54	69	80	75	79	82	67
HIV1MN	0	0	30	36	ND	ND	ND	ND	34
HIV1RF	0	0	67	63	ND	ND	ND	ND	65
HIV1SF2	0	0	9	66	ND	ND	ND	ND	58
DP116	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	75	ND	ND	ND	ND	ND	ND	ND	67
HIV1MN	35	ND	ND	ND	ND	ND	ND	ND	34
HIV1RF	81	ND	ND	ND	ND	ND	ND	ND	65
HIV1SF2	81	ND	ND	ND	ND	ND	ND	ND	58

FIG.4A

DP180	40	20	10	5	2.5	1.25	0.625	0.3125	Control
<i>Syncytia</i>									
HIV1LAT	50	>45	>45	>45	>45	>45	>45	>45	58
DP185	40	20	10	5	2.5	1.25	0.625	0.3125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	0	0	0	0	0	ND	60

FIG.4B

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<u>HIV1</u>								
Number of Syncytia/well: concentration in ng/ml (nanograms/ml)								
DP178	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV1	0	0	0	0	0	14	20	48
DP116	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV1	ND	48	ND	ND	ND	ND	ND	ND
<u>HIV2</u>								
Number of Syncytia/well: concentration in μ g/ml (micrograms/ml)								
DP178	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV2	50	54	55	57	63	77	78	76
DP116	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV2	ND	58	ND	ND	ND	ND	ND	ND

FIG.5

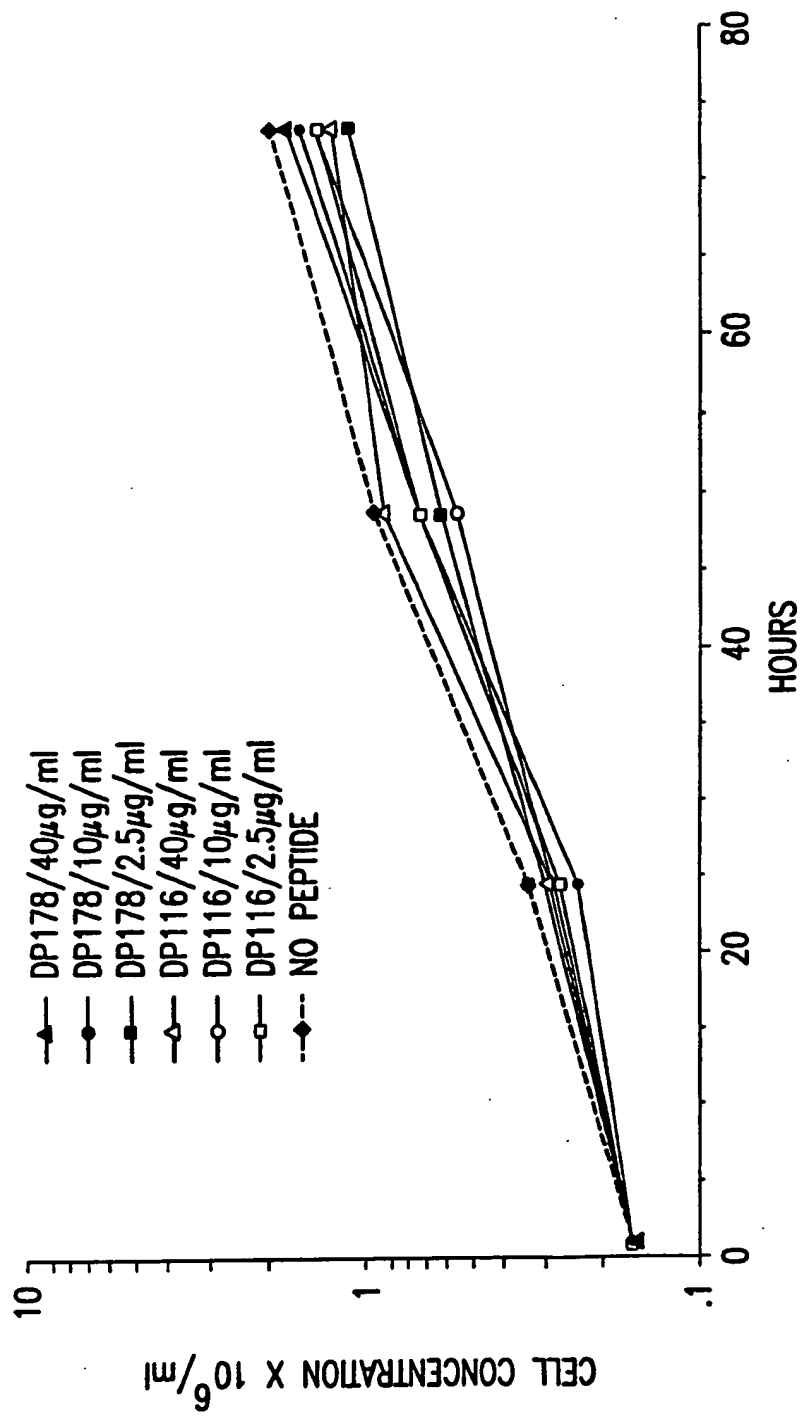


FIG.6

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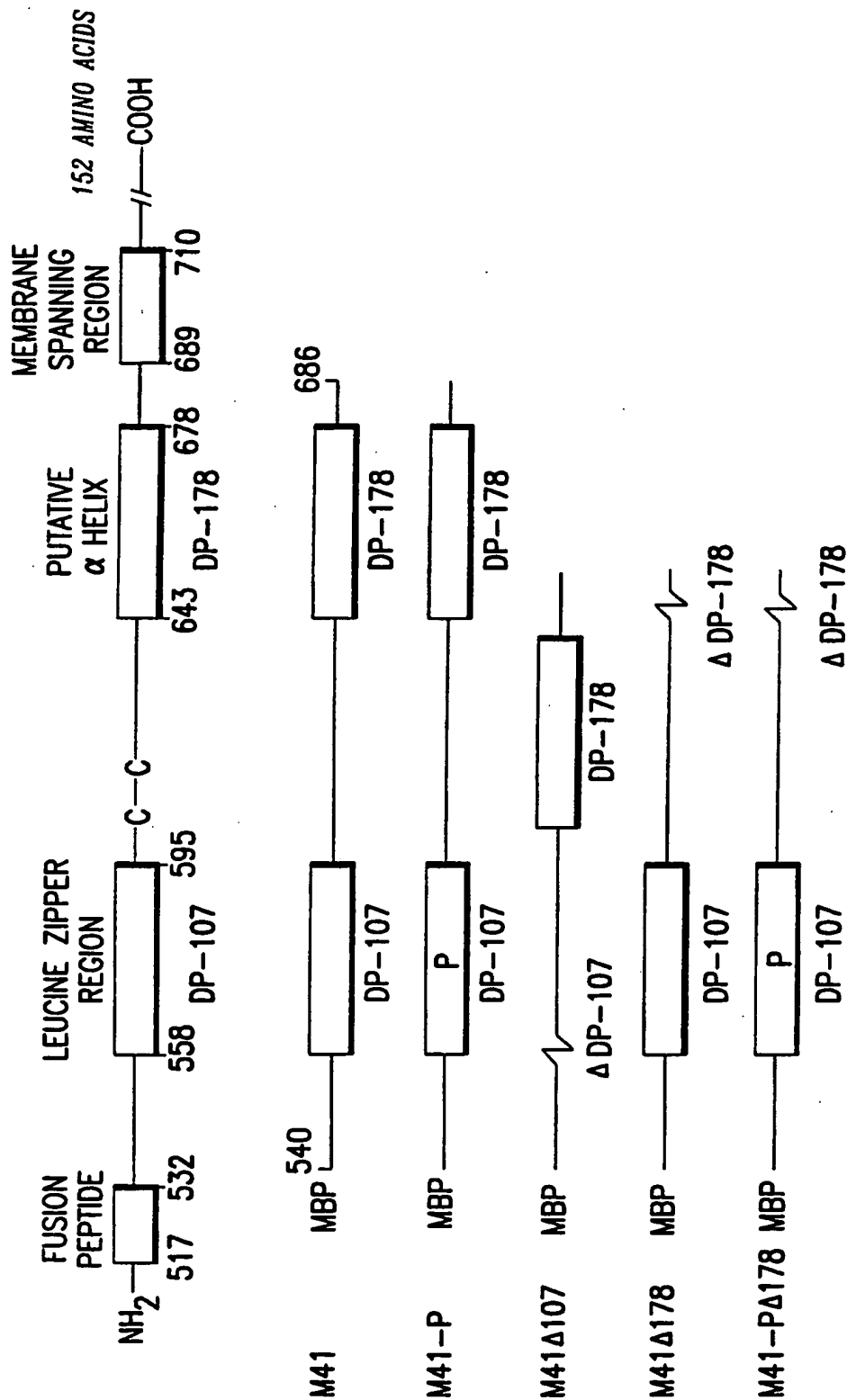


FIG.7

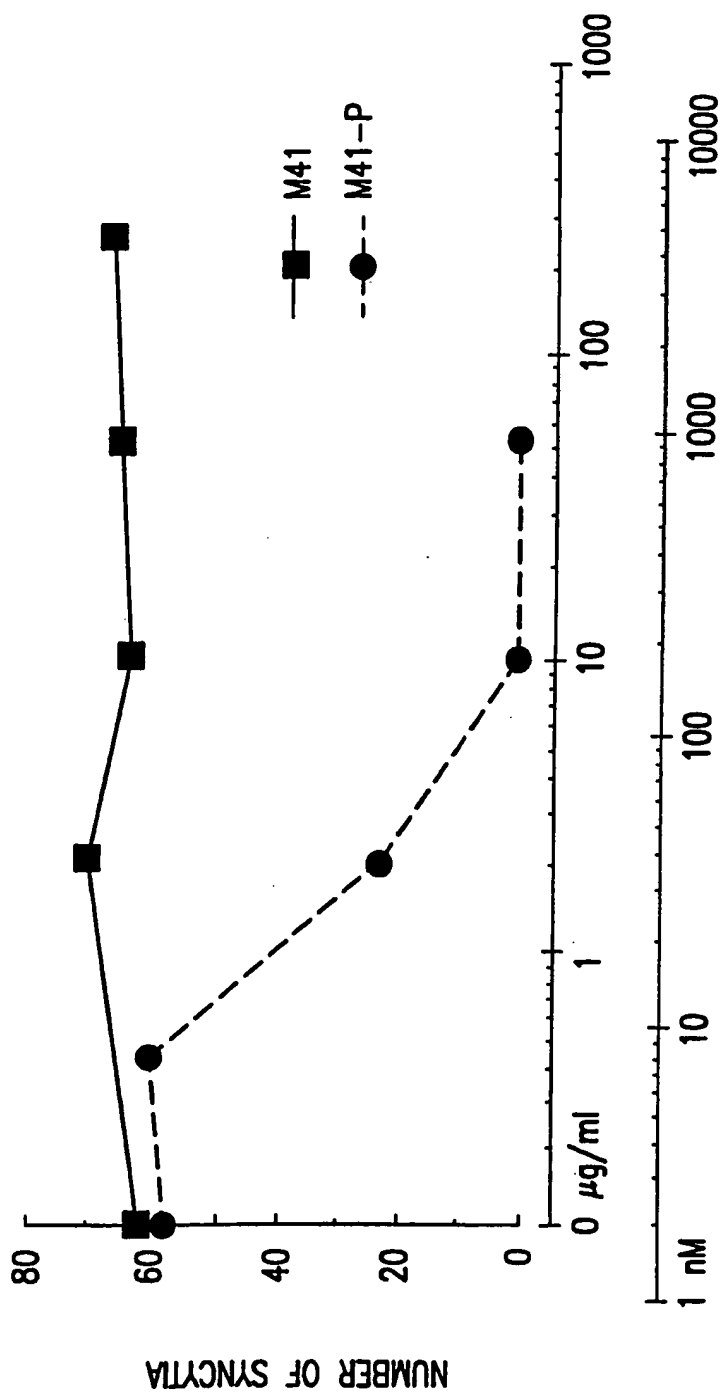


FIG.8

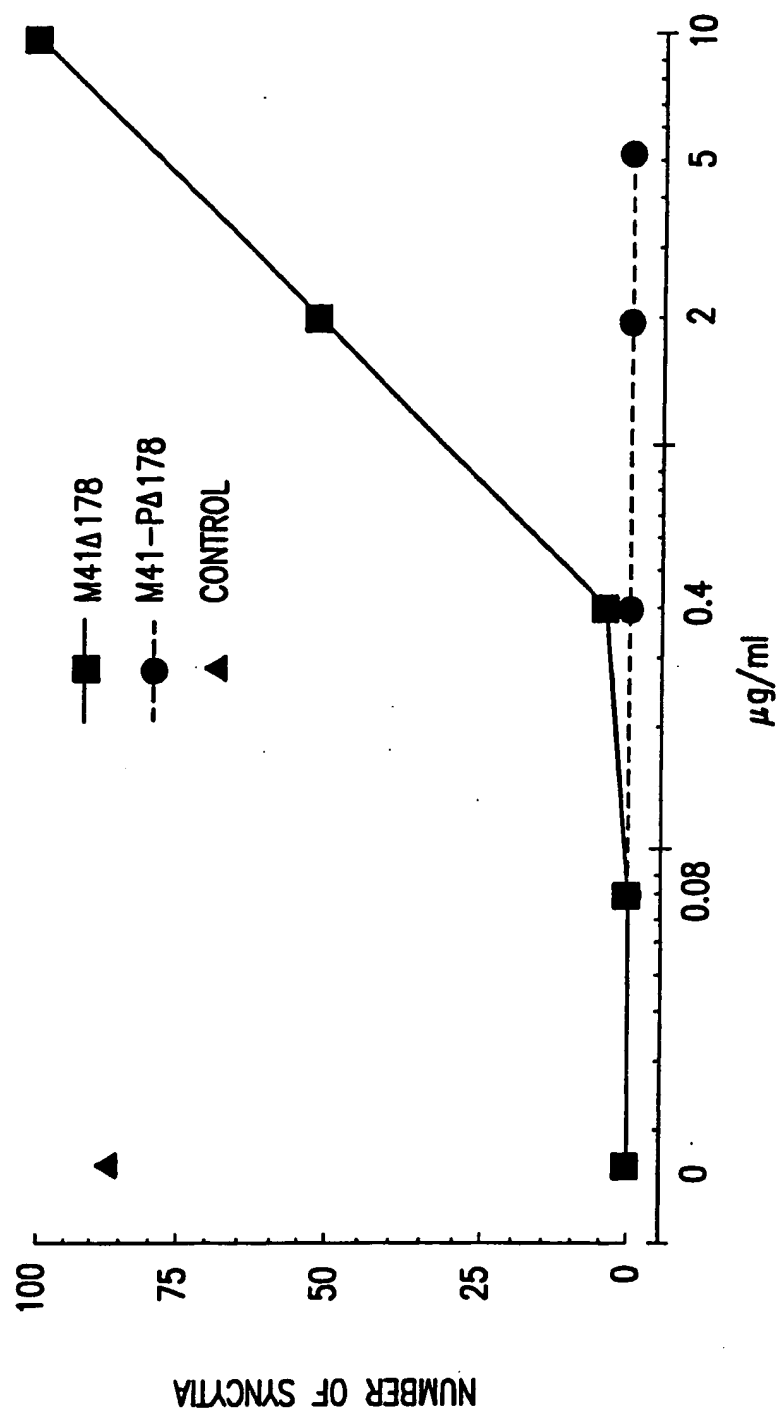


FIG.9

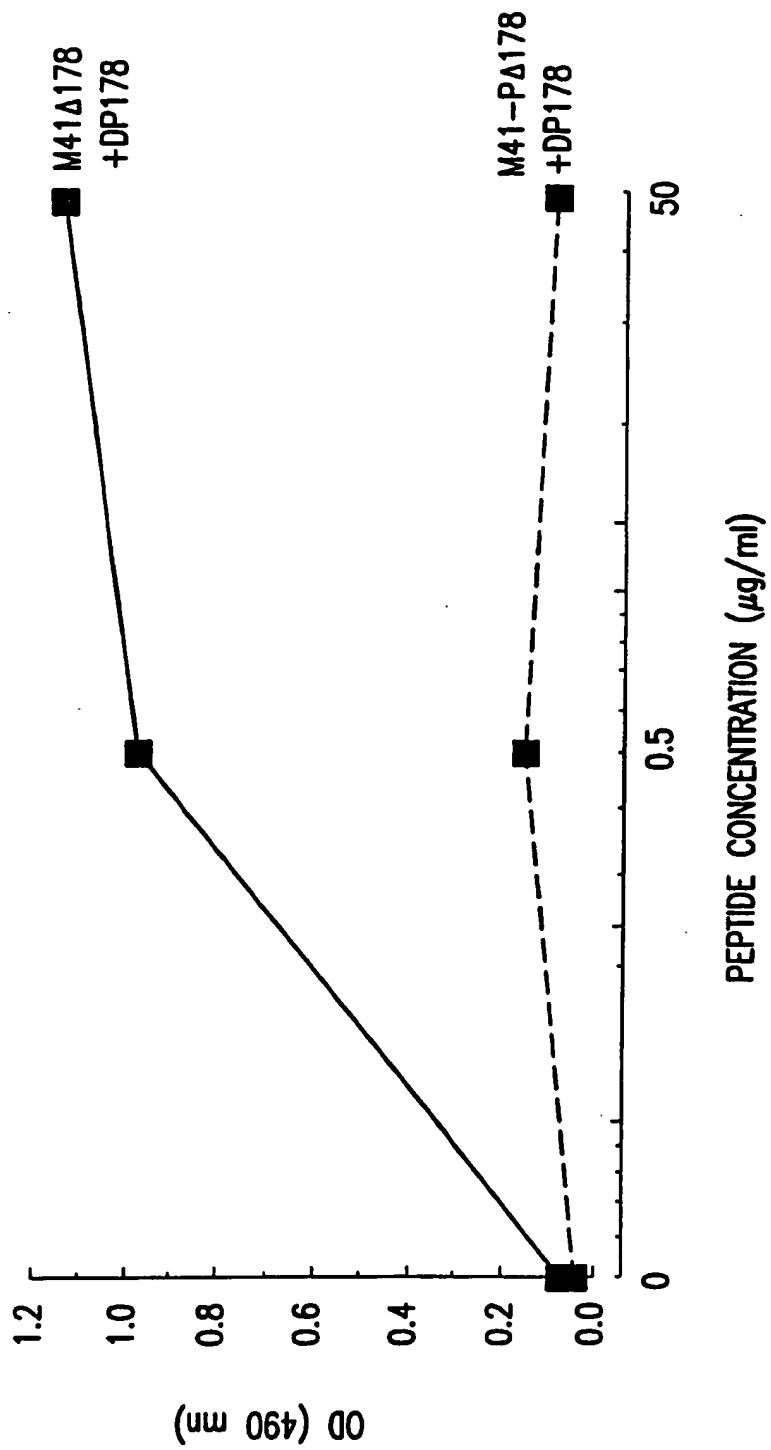


FIG.10

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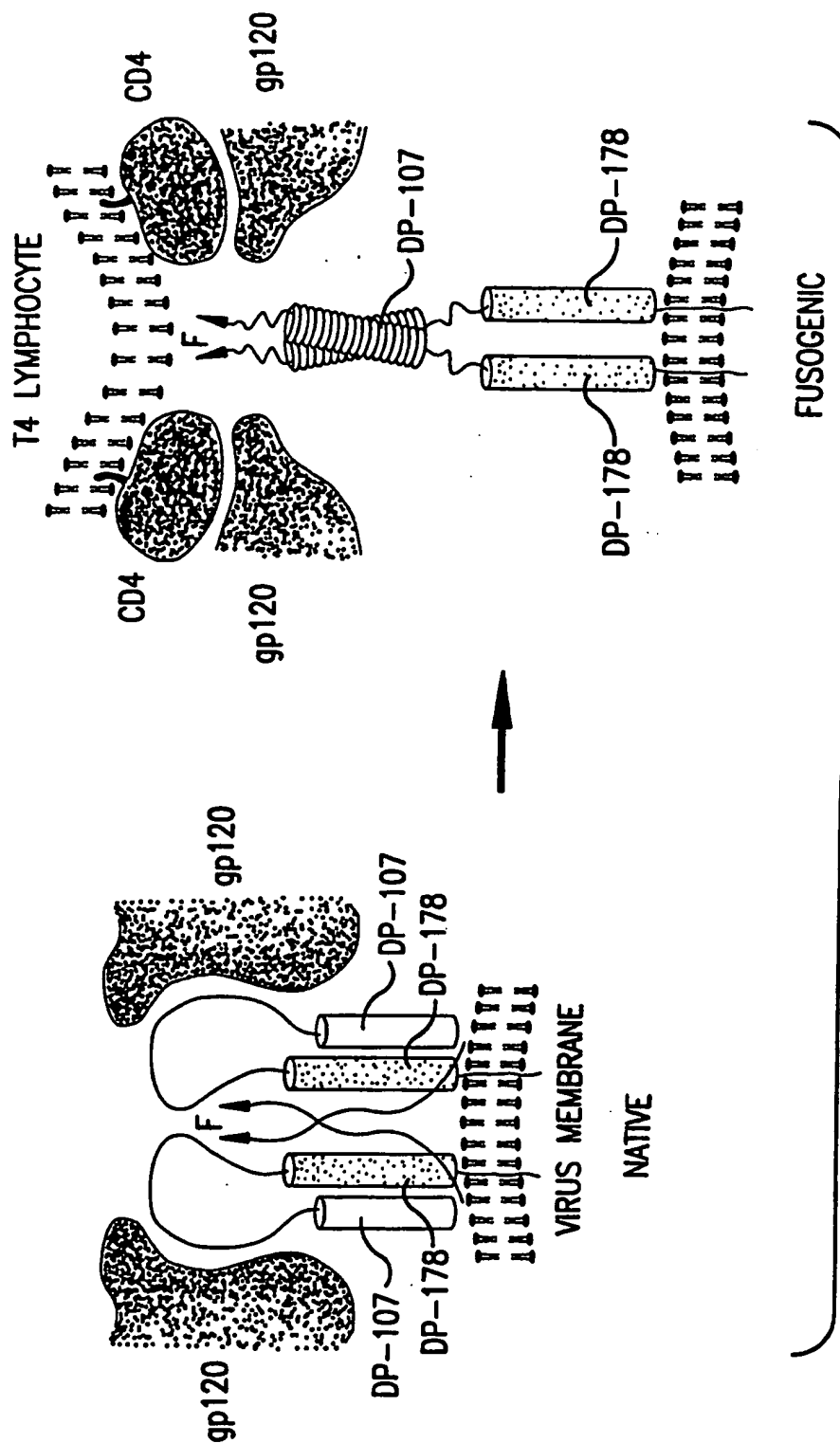
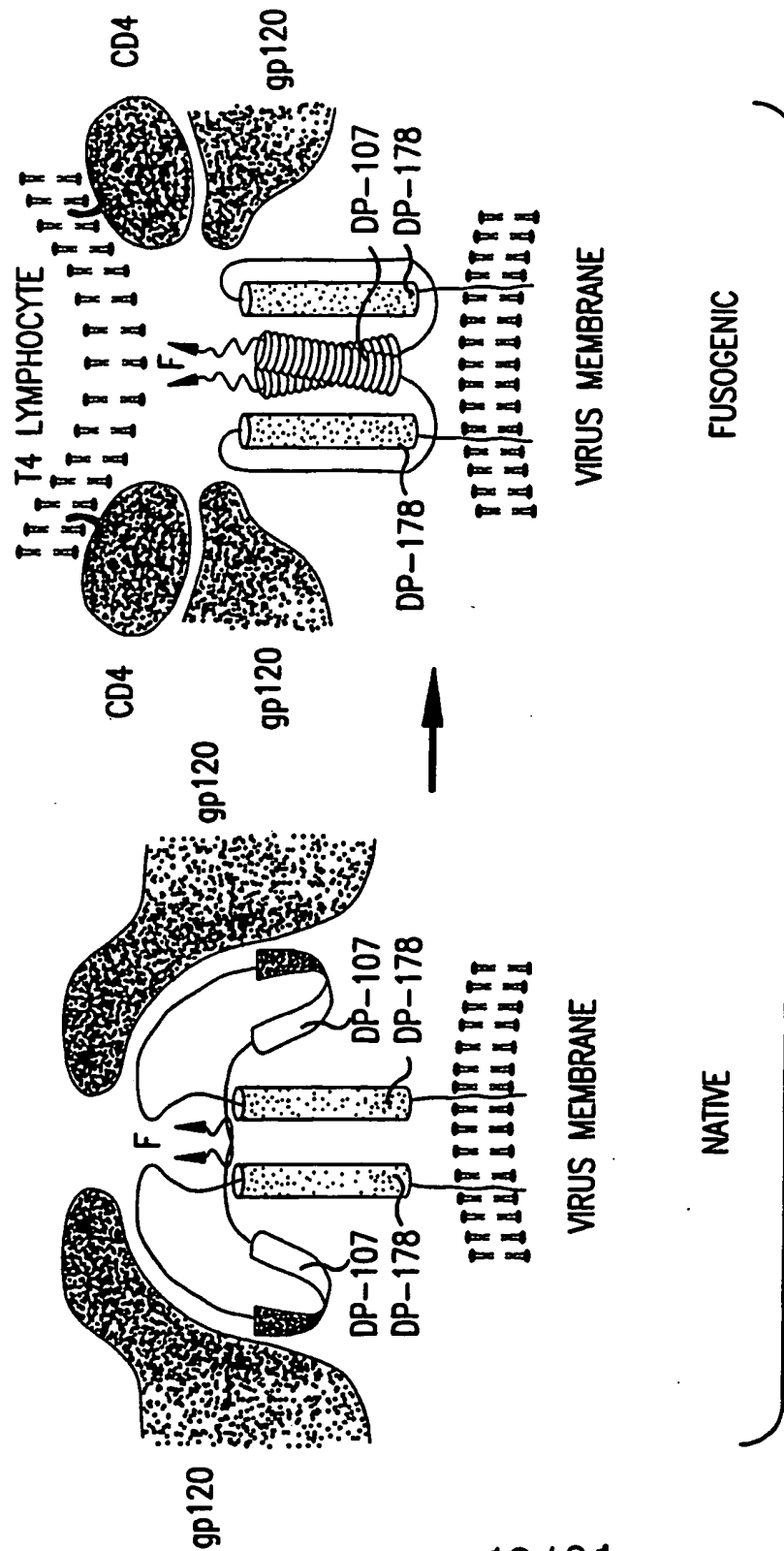


FIG.11A



Sequence	Positions														Motifs			
	A	D	A	D	A	D	A	D	A	D	A	D	A	D				
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	{LNNV} {CFGIMPVW}		
C-FOS (fos_human)	T	D	T	L	Q	A	E	T	D	Q	L	E	D	E	K	{IKLT} {CFGIMPVW}		
C-JUN (tap1_human)	I	A	R	L	E	E	K	V	K	T	L	L	K	A	Q	{AILNV} {CDFGHILPVW}		
C-MYC (myo_human)	E	Q	K	L	I	S	E	E	D	L	L	E	K	R	E	{ELR} {ACFGMPVW}		
FLU LOOP 36	I	E	K	T	N	E	K	F	H	Q	I	E	K	E	F	{FILTV} {ACFLMPTVW}		

FIG.12

Sequence	A	D	A	D	A	D	A	D	A	D	A	D	A	D	Motifs
DP-107 (env_hv1bru)L1=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	[ILQT] {CFIMPSTY}
DP-107 (env_hv1bru)L1=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	[ILQTV] {CDFIMPST}
DP-107 (env_hv1bru)L1=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	[ILQTV] {CDFIMPST}
DP-107 (env_hv1bru)L2=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	[EKLNOV] {CDFKMPSTY}
DP-107 (env_hv1bru)L2=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	[EKLNOV] {CFKMPST}
DP-107 (env_hv1bru)L2=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	[EKLNOV] {CFKMPST}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EKLQY] {ACFGMPRVWY}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EKLQWY] {CFGMPRVY}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EFKLOWY] {CFGMPRVY}
DP-178 (env_hv1bru)Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EILNQSY] {ACFGMPRVWY}
DP-178 (env_hv1bru)Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EILNQSWY] {CFGMPRVY}
DP-178 (env_hv1bru)Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EFILNQSWY] {CFGMPRVY}

FIG.13

Sequence	Positions												Parent Motif	Hybrid Motif																							
	A	D	A	D	A	D	A	D	A	D	A	D																									
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	L	L	S	K	N	Y	H	L	E	N	E	V	A	R	L	K	K	L		[LMNV] {CFGIMPTW}								
DP-107 (env_hv1bru)L1=0	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I		[ILOTV] {CFIMPST}	[ILMNQTV] {CFIMPT}							
DP-107 (env_hv1bru)L1=0	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L			
DP-107 (env_hv1bru)L1=0	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q
DP-107 (env_hv1bru)L2=0	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I										
DP-107 (env_hv1bru)L2=0	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L			
DP-107 (env_hv1bru)L2=0	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q

FIG. 14

Sequence	Positions																								Parent Motif	Hybrid Motif																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	L	L	S	K	N	Y	H	L	E	N	V	A	R	L	K	K	L																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														

FIG. 15

Sequence	Positions																Parent Motif	Hybrid Motif																						
	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D																								
DP-107 (env_hv1bru) L1=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	A	V	E	R	Y	L	K	D	Q	[ILOTV] {CDFIMPST}						
DP-107 (env_hv1bru) L2=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	A	V	E	R	Y	L	K	D	Q	[EKLQW] {CFKQPS}						
DP-178 (env_hv1bru) Y1=A	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	[EFKLQWY] {CFGMPRVY}				
DP-178 (env_hv1bru) Y1=D					Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	[EFILQSWY] {CFGMPRVY}
FLU LOOP 36	I	E	K	T	N	E	K	F	H	Q	I	E	K	E	F	S	E	V	E	G	R	I	Q	D	L	E	K	Y								[FILTV] {ACFLMPTVW}				

FIG.16

Sequence	Positions																Parent Motif	Hybrid Motif
	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D		
GCN4 (gcn4 yeast)	MKQLLEDKVEE	L	SKN	YHL	ENE	V	ARL	KKL									[LMNV] {CFGIMPTW}	
DP-107 (env_hv1bru)L1=D	NNLLRAIEAQ	H	LL	QL	TV	W	GI	KQL	Q	A	R	I	L	A	V	E	R	[ILOTV] {CDFIMPST}
DP-178 (env_hv1bru)Y1=A	YTSLSLIMS	L	IE	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	[EFKLOWY] {CFGMPRVY}
GCN4 (gcn4 yeast)	MKQLLEDKVEE	L	SKN	YHL	ENE	V	ARL	KKL									[LMNV] {CFGIMPTW}	
DP-107 (env_hv1bru)L1=D	NNLLRAIEAQ	H	LL	QL	TV	W	GI	KQL	Q	A	R	I	L	A	V	E	R	[ILOTV] {CDFIMPST}
DP-178 (env_hv1bru)Y1=D	YTSLSLHSL	I	EE	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	[EFILNOSWY] {CFGMPRVY}
GCN4 (gcn4 yeast)	MKQLLEDKVEE	L	SKN	YHL	ENE	V	ARL	KKL									[LMNV] {CFGIMPTW}	
DP-107 (env_hv1bru)L2=D	NNLLRAIEAQ	H	LL	QL	TV	W	GI	KQL	Q	A	R	I	L	A	V	E	R	[EKLNV] {CFKMP}
DP-178 (env_hv1bru)Y1=A	YTSLSLHSL	I	EE	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	[EFKLOWY] {CFGMPRVY}
GCN4 (gcn4 yeast)	MKQLLEDKVEE	L	SKN	YHL	ENE	V	ARL	KKL									[LMNV] {CFGIMPTW}	
DP-107 (env_hv1bru)L2=D	NNLLRAIEAQ	H	LL	QL	TV	W	GI	KQL	Q	A	R	I	L	A	V	E	R	[EKLNV] {CFKMP}
DP-178 (env_hv1bru)Y1=D	YTSLSLHSL	I	EE	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	[EFILNOSWY] {CFGMPRVY}

FIG.17

Sequence	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	Parent Motif	Hybrid Motif
UCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	L	L	S	K	N	L	L	Y	H	[LMNV] {CFGIMPSTW}	
DP-107 (env_hv1bru) L1=D		N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	[ILQTV] {CDFIMPST}	
DP-107 (env_hv1bru) L2=D		N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	[EKLNV] {CFKUPS}	
DP-178 (env_hv1bru) Y1=A	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	E	K	N	E	[EFKLVW] {CFGMPRVY}	
DP-178 (env_hv1bru) Y1=D		Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	E	K	N	[EFILNDSWY] {CFGMPRVY}	
C-FOS (fos_human)	T	D	T	L	Q	A	E	T	D	Q	L	E	D	E	K	S	A	L	[IKLT] {CFCHIMPSTW}	
C-JUN (top1_human)	I	A	R	L	E	E	K	V	K	T	L	K	A	Q	N	S	E	L	[AILNV] {CDFGHILPSTW}	
C-MYC (myo_human)	E	Q	K	L	I	S	E	E	D	L	L	E	K	R	R	E	Q	L	[ELR] {ACFGMPRVY}	
FLU LOOP 36	I	E	K	T	N	E	K	F	H	Q	I	E	K	E	F	S	E	V	[FILTV] {ACEIMPSTW}	
																			[AEFIKLMNORSTVWY] {CFP}	
																			= {CDGHP} {CFP}	

FIG.18

P-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(1)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(2)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(3)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(4)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(5)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(6)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(7)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(8)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(9)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-{P}(10)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-X(1,12)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
 P-X(13,23)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]

FIG.19

Fusion ♥ALLMOTI5♥
 Peptide ♣107x178x4♣
 ♥.....ELGELG A AGSTMGARSM TLTVQARQ ♣LLSGIVQQQ DPI07-NNL

LRAIEAQOHL LOLTWGIKO LOARILAYER YLKDQ-DPI07 QLLG♥♥ I WGC

♥ALLMOTI5♥ ♣107x178x4♣
 LVS Coiled-Coil
 SGKLICT TAVP ♥WNASWS NKSLEQIWNN MTWM *E ♣WDREINN DPI78-

YTSLIHSL IEESONOOEK NEOELLELDK* WASLWNWF-DPI78 NI

♦Transmembrane Region♦
 TNWLWYIK♣ ♦IEIMIVGGLVGLRIVEAVLSIV NRVROGYS♥ PL

♣P23LZIPC♣
 SFQTHLPTPR GPDR ♣PEGIEE EGGERDRDRS IRLVNGSLAL IWDDLRLSL♣ CL

♥ALLMOTI5♥ ♣107x178x4♣
 F ♥SYHRLRDL L LIVTRIVELL GRRGW ♣EALKYWWNLLOYWSQ

ELKNSAVSLLNAT♣ AIAVAEG TDRVIEVVQG A♥ CRAIRHIPR

RIRQGLERIL L

FIG. 20

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SUBSTITUTE SHEET (RULE 26)

Fusion ♡ ALLMOTI5 ♡
 Peptide ♡107x178x4 ♡
 ♡.....ELGEL LGVGSALAS GVA ♡VSKVLHLEGEVNIKSA

♡P1&12LZIPC ♡
LLSTNKA VVS LSNGVSVLTS KVLDLKNIYD KQ ♡ ♡ LL ♡PIVNKQ

♡107x178x4 ♡
 SC ♡SISNIETV I ♡ EEOOKNNRLLETREFSVNAG ♡ VTPVSTMLTNSELLSL

♡P1&12LZIPC ♡
 ♡ ALLMOTI5 ♡
 INDM ♡PI ♡TNDQ KKLMSNNVQI V ♡ RQSYSI ♡ MS IIKEEVLAYV

VQ ♡ LPLYGVID TPCWKLHTSP LCTTNTKEGS NICLTRTDRG WYCDNAGSVS

FFPQAETCKV QSNRVFCDTM NSLTLPSEIN LCNVDIFNPK

YDCKIMTSKT DVSSSVITSL GAIVSCYGKT KCTASNKNRG

IIKTFSNGCDYVSNKGMDTV SVGNTLYYVN KQEGKSLYVK G

♡P7, 12, & 23LZIPC ♡
 ♡107x178x4 ♡ ♡ ALLMOTI5 ♡
 EPIINFYDPLVF ♡PSDE ♡EDASISQVNEKINOSLAF ♡I ♡ RKSDELL ♡

♡Transmembrane Region ♡
HNVNA ♡ GK STTN ♡IMITLIIVIIIVILLS LIAVGLLLY ♡ C ♡

KARSTPVTLS KDQLSGINNI AFSN

FIG. 21

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SUBSTITUTE SHEET (RULE 26)

Fusion
 Peptide ♡ALLMOTI5♡ ♡107x178x4♡
FLGFLG ♡AAGTA MGAAA ♡TALTVOSQHLLAGILOQQKNLLAAV

♡107x178x4♡
EAQ ♡ QQM ♡LKLTIWGVKNLNARVTALEKYLEDOARLN ♡ AWG♡ CA

LVS Coiled-Coil
 ♡ALLMOTI5♡ ♡107x178x4♡
 WKQVCHTTVP WQWNNRTPDW ♡NNMT *WLE ♡WEROISYLEGNTT

♡107x178x4♡
TOLEEARAQEEKNLD ♡ AYOKLSS* WSDFWWSW♡ FDF ♡SKWLN ♡ILK

♦Transmembrane Region♦
IGFLDVLGIGLRLLYTV ♦ YS ♡ CIARVRQGYS PLSPQIHHP WKGQPDNAEG

PGEGGDKRKN SSEPWQKESG TAEWKS NWCK RL TNWCSISS IWLYNS

♡ALLMOTI5♡
 ♡CLTL LVHLRSAFQY IQYGLGELKA AAQEAVVALA RLAQNAGYQIWL♡

ACRSAYRA IINSPRRVRQ GLEGILN

FIG. 22

Fusion ♣107x178x4♣
 Peptide ♥ALLMOTIS♥ *LVS Coiled-Coil*
EAG ♥VYL AGVALGVATA AQITAGIALHQ ♣*SNLNAQAIQ

SLRTSLEQSNKAIEEIREATOETVIA* VOGVQDY♣ VNNEL♥ VP

♥ALLMOTIS♥

♣107x178x4♣

♣P6 & 12LZIPC♣

AMQHMSCELVGQRLGLRLLRYYTELLSIFGPSLRD ♣PISA ♣♥EISIQALIVAL

GGEIHKILEKLGYSGSD♣ MIAILES RGIKTKI♥ THVDLPGKF ILSISY

♣P1 & 12LZIPC♣
 ♣PTLSEVKGIVHRLEAV♣ SYNIGSQEWYTTVPRYIATNGYLISNFDDESSCVFVS

ESAICSQNSL YPMSPLLQQC IRGDTSSCAR TLVSGTMGNK FILSKGNIVA

NCASILCKCY STSTINQSP DKLLTFLASD TCPLVEIDGA TIQVGGRQYP

LVS Coiled-Coil
 ♥ALLMOTIS♥
 ♣P12 & 23LZIPC♣

DMVYEGKVAL G ♣PAISLD ♥RL*DVGTNLGNALKKLD DAKVLI♣

♦Transmembrane Region♦

DSS♣ NOILETVRRS♥* SFN ♦EGSLLSVPILSCTALALLLLIYCC♦

K RRYQQTLKQH TKVDPAFKPD LTGTSKSYVR SL

FIG. 23

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SUBSTITUTE SHEET (RULE 26)

Fusion ♥ALLMOTIS♥
 Peptide ♣107x178x4♣
 ♥.....FIGAI IGSVALGVA TAAQITAASA LIQANQNAAN ♣ILRLKESITA

TIEAVHEVTDGLSQLAVA♣ VG KM♥ QQFVNDQFNNTAQELDCIKITQQV

♥ALLMOTIS♥
 GVELNLYLTELT TV FGPQITSPAL ♥TQLTIQALYNAGGNMDYLLTKLGVG

♣P1 & 12LZIPC♣
 NNQLSSLIGSGLIT GN♥ ♣PILYDSQT QLLGIQVTLP SVGNLNNMRATYLET

LSVST TKGFASALVP KVVVTQVGSVI EELDTSYCIE TDLDLYCTRI VTFPMSPGIY

SCLNGNTSAC MYSKTEGALT TPYMTLKGSV IANCKMTTCR CADPPGIISQ

♥ALLMOTIS♥
 ♣107x178x4♣
 NYGEAVSLID RHSCN ♣♥VLSLD GITLRLSGEF DATYQKNISI LDSQVIVTG

LVS Coiled-Coil ♦Trans-
 NLDISTELGNV NNSISNALDK LEESNSKLDK VNVKLTSTSA ♦LIT YIA

membrane Region♦
LTAISLVCGLSLV♥♣ LACYLMY♦ KQKAQQKTLLWLGNNILGQMRATTKM

FIG. 24

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Fusion ♥ALLMOTIS♥
 Peptide ♣107x178x4♣ *LVS Coiled-Coil*
EEGGV ♣IG ♥TIALG *YATSAQITAAYALVEAKQARSDIEKLKE

AIRDTNKAVOSVOSSIGNLIVAIKSVQ* DYVNKE♥♣ IVPSIARLGCEAAG

♥ALLMOTIS♥
 ♣107x178x4♣
 LQLGIALTQH ♣♥YSELTNIEGDNIGSLOEKGIKLOGIASLYRTNITE♥♣

♣P5 & 12LZIPC♣
 IFTTSTVDKYDIYDLLFTESIKVRVIDVDLNDYSITLQVRL ♣PLLTRLNTQIYR

VDSISYNI♣ QNREWI♣ PLPSHIMTKGAFLGGADVKECIEAFSSYIC

PSDPGFVLNHEMESCLSGNISQCPRTVVKSDIVPRYAFVNGGVVANCITT

TCTCNGIGNRINQPPDQGVKIITHKECNTIGINGMLFNTNKEGTLAFYTP

♥ALLMOTIS♥
 ♣107x178x4♣
 ♣P6 & 23LZIPC♣
 NDITLNNVALD ♣PIDI ♣SIELN ♥KAKSDLEESKEWI♣ RRSNOKL♣

♦Transmembrane Region♦
DSIGNWHOSSIT ♦IIIV♣ LIMIIILEHINVTII♦ IIHVKY♥ R
 IQKRNRVDQN DKPYVLTK

FIG. 25

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Fusion
Peptide
.....GLFGAI AGFIENGWEGMIDGWYGFRHQNSEGTG

♠107x178x4♠

♥ALLMOTI5♥

LVS Coiled-Coil

*Q ♥AADLKST ♠QAAIDQINGKLNRVIEKTNEKTHQIEKEESEVEGRIQ

DLEKYYEDTKIDL* WSYNAELLVALENQETI♠ DLT♥ DSEMKNLFETR

RQLRENAEEMGNGCFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKG

VELKSGYKDWILWISFAISCFLLCVLLGFIMWACQRGNIRCNICI

FIG. 26

AV	CD	RSV F2	YTSVITIELSNIKENKCNCTDAKVKL IKQELDKYKNVTELOLLMOST
+	+ / ++	T-142	YTSVITIELSNIKENKCNCTDAKVKL IKQELDKYK
++	+ / +++	T-143	TSVITIELSNIKENKCNCTDAKVKL IKQELDKYKN
+	+ / ++	T-144	SVITIELSNIKENKCNCTDAKVKL IKQELDKYKNA
-	+ / +	T-145	VITIELSNIKENKCNCTDAKVKL IKQELDKYKNV
-	+ / -	T-146	ITIELSNIKENKCNCTDAKVKL IKQELDKYKNV
-	-	T-147	TIIELSNIKENKCNCTDAKVKL IKQELDKYKNVTE
-	-	T-148	IELSNIKENKCNCTDAKVKL IKQELDKYKNVTELO
-	+ / -	T-149	ELSNIKENKCNCTDAKVKL IKQELDKYKNVTELO
-	-	T-150	LSNIKENKCNCTDAKVKL IKQELDKYKNVTELOL
-	+ / +	T-151	SNIKENKCNCTDAKVKL IKQELDKYKNVTELOLL
-	+ / ++	T-152	NIKENKCNCTDAKVKL IKQELDKYKNVTELOLLM
-	+ / +	T-153	IKENKCNCTDAKVKL IKQELDKYKNVTELOLLMQ
-	+ / ++	T-154	KENKCNCTDAKVKL IKQELDKYKNVTELOLLMQS
-	+ / +	T-155	ENKCNCTDAKVKL IKQELDKYKNVTELOLLMOST

FIG.27

AV	CD	RSV	
++	+/-	T-67	DEFDASISQWNEKINQSLAF IRKSDELL
		F1-178	GEPIINFYDPLVPSDEFDASISQWNEKINQSLAF IRKSDELLHNNWAGKSTT
+/-		T-104	IIINFYDPLVPSDEFDASISQWNEKINQSLAF IRK
+/-		T-105	INFYDPLVPSDEFDASISQWNEKINQSLAF IRKS
+/-		T-106	NFYDPLVPSDEFDASISQWNEKINQSLAF IRKSD
+		T-107	FYDPLVPSDEFDASISQWNEKINQSLAF IRKSDE
++		T-108	YDPLVPSDEFDASISQWNEKINQSLAF IRKSDEL
++		T-109	DPLVPSDEFDASISQWNEKINQSLAF IRKSDELL
+		T-110	PLVPSDEFDASISQWNEKINQSLAF IRKSDELLH
++		T-111	LVFPSDEFDASISQWNEKINQSLAF IRKSDELLHN
++	+/-	T-112	VFPSDEFDASISQWNEKINQSLAF IRKSDELLHNV
++	+/-	T-113	FPSDEFDASISQWNEKINQSLAF IRKSDELLHNVN
++	+/-	T-114	PSDEFDASISQWNEKINQSLAF IRKSDELLHNVNA
++	+/-	T-115	SDEFDASISQWNEKINQSLAF IRKSDELLHNVNAG
++	+/-	T-116	DEFDASISQWNEKINQSLAF IRKSDELLHNVNAGK
++	+/-	T-117	EFDASISQWNEKINQSLAF IRKSDELLHNVNAGKS
++	+/-	T-118	FDASISQWNEKINQSLAF IRKSDELLHNVNAGKST
++	+/-	T-119	DASISQWNEKINQSLAF IRKSDELLHNVNAGKSTT

(T-67 LIKE)

FIG.28

AV	CD	HPF 3 178	YTPNDITLNNVALDPIDISIELNKAQSDLEESKEWIRRSNQKLDISIGNWHOSSTT
-	-	189	YTPNDITLNNVALDPIDISIELNKAQSDLEESKE
-	-	190	TPNDITLNNVALDPIDISIELNKAQSDLEESKEW
-	-	191	PNDITLNNVALDPIDISIELNKAQSDLEESKEWI
-	-	192	NDITLNNVALDPIDISIELNKAQSDLEESKEWIR
-	+/-	193	DITLNNVALDPIDISIELNKAQSDLEESKEWIRR
+/-	+/-	194	ITLNNVALDPIDISIELNKAQSDLEESKEWIRRS
+/-	+/+	195	TLNNVALDPIDISIELNKAQSDLEESKEWIRRSN
+	+/+	196	LNNVALDPIDISIELNKAQSDLEESKEWIRRSNQ
+	+/+	197	NNVALDPIDISIELNKAQSDLEESKEWIRRSNQK
+++	+/+	198	NSVALDPIDISIELNKAQSDLEESKEWIRRSNQKL
++	+/+	199	SVALDPIDISIELNKAQSDLEESKEWIRRSNQKLD
-		200	VALDPIDISIELNKAQSDLEESKEWIRRSNQKLD
+++		201	ALDPIDISIELNKAQSDLEESKEWIRRSNQKLD
+++		202	LDPIDISIELNKAQSDLEESKEWIRRSNQKLD
+++		203	DPIDISIELNKAQSDLEESKEWIRRSNQKLD
+++		204	PIDISIELNKAQSDLEESKEWIRRSNQKLD
+++		205	IDISIELNKAQSDLEESKEWIRRSNQKLD
+		206	DISIELNKAQSDLEESKEWIRRSNQKLD
+		207	ISIELNKAQSDLEESKEWIRRSNQKLD
+		208	SIELNKAQSDLEESKEWIRRSNQKLD
++		209	IELNKAQSDLEESKEWIRRSNQKLD
++		210	ELNKAQSDLEESKEWIRRSNQKLD

FIG.29

CD	HPF3 107	GTIALGVATSAQITA AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA I KSVQDYVNKE IVP
+/+	157	ALGVATSAQITA AVALVEAKQARSDIEKLKEAIRD
+/+	158	LGVATSAQITA AVALVEAKQARSDIEKLKEAIRDT
+/-	159	GVATSAQITA AVALVEAKQARSDIEKLKEAIRDTN
+/+	160	VATSAQITA AVALVEAKQARSDIEKLKEAIRDTNK
+/+	161	ATSAQITA AVALVEAKQARSDIEKLKEAIRDTNKA
+/-	162	TSAQITA AVALVEAKQARSDIEKLKEAIRDTNKAV
+/+	163	SAQITA AVALVEAKQARSDIEKLKEAIRDTNKAVQ
+/+++	164	AQITA AVALVEAKQARSDIEKLKEAIRDTNKAVQS
+/+	165	QITA AVALVEAKQARSDIEKLKEAIRDTNKAVQSV
+/-	166	ITA AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQ
+/-	167	TAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQS
+/-	168	AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS
+/-	169	AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSI
+/-	170	VALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIG
+/-	171	ALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGN
+/-	172	LVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNL
+/-	173	VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI
+/++	174	EAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIV
T-40		AKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA
+/++	175	KQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAI
+/+++	176	QARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIK
+/-	177	ARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKS
+/-	178	RSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSV
-	179	SDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQ
-	180	DIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQD
-	181	IEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDY
-	182	EKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYV
+/++	183	KLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVN
+/+++	184	LKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNK
-	185	KEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKE
-	186	EAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEI
-	187	AIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV
-	188	IRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIVP

FIG.30

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SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/05739

A. CLASSIFICATION OF SUBJECT MATTER IPC(S) : A61K 37/02, 39/12; C12Q 1/70; G01N 33/53 US CL : 424/88, 89; 435/5, 7.1, 7.92-7.95, 974; 530/324-331, 333, 334 According to International Patent Classification (IPC) or to both national classification and IPC																								
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/88, 89; 435/5, 7.1, 7.92-7.95, 974; 530/324-331, 333, 334 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS, Biosis																								
C. DOCUMENTS CONSIDERED TO BE RELEVANT																								
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																						
NONE	NONE	NONE																						
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																								
<table border="0"><tr><td>* Special categories of cited documents:</td><td>* I</td><td>later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td></tr><tr><td>* A</td><td>document defining the general state of the art which is not considered to be of particular relevance</td><td></td></tr><tr><td>* E</td><td>earlier document published on or after the international filing date</td><td>* X</td><td>document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td></tr><tr><td>* L</td><td>document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td><td>* Y</td><td>document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td></tr><tr><td>* O</td><td>document referring to an oral disclosure, use, exhibition or other means</td><td>* G</td><td>document member of the same patent family</td></tr><tr><td>* P</td><td>document published prior to the international filing date but later than the priority date claimed</td><td></td><td></td></tr></table>			* Special categories of cited documents:	* I	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	* A	document defining the general state of the art which is not considered to be of particular relevance		* E	earlier document published on or after the international filing date	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	* L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	* O	document referring to an oral disclosure, use, exhibition or other means	* G	document member of the same patent family	* P	document published prior to the international filing date but later than the priority date claimed		
* Special categories of cited documents:	* I	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention																						
* A	document defining the general state of the art which is not considered to be of particular relevance																							
* E	earlier document published on or after the international filing date	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone																					
* L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art																					
* O	document referring to an oral disclosure, use, exhibition or other means	* G	document member of the same patent family																					
* P	document published prior to the international filing date but later than the priority date claimed																							
Date of the actual completion of the international search 07 SEPTEMBER 1994		Date of mailing of the international search report 26 SEP 1994																						
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer JEFFREY STUCKER Telephone No. (703) 308-0196																						

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/05739

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 2
because they relate to subject matter not required to be searched by this Authority, namely:
that the claimed subject matter is directed to mental processes.
2. ☒ Claims Nos.: 13-16 and 42-49
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
because the sequences have not been submitted to the International Searching Authority in electronic form.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.